

2.81 (2H, t, J=7.3Hz), 3.09 (2H, t, J=7.3Hz), 3.69 (2H, br s),  
4.39 (2H, s), 6.49 (1H, s), 9.81 (1H, s).

MS (FD) m/z: 295M<sup>+</sup>.

[Referential Example 341] 1-[3-(5-tert-Butoxycarbonyl-  
5 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 321, a  
reaction was effected using 3-(5-tert-butoxycarbonyl-  
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propanal and 1-  
10 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride  
as starting materials, whereby the title compound was  
obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 (9H, s), 1.69-1.79 (2H, m),  
2.36 (2H, t, J=7.3Hz), 2.49-2.54 (4H, m), 2.65-2.75 (4H, m),  
15 3.10 (4H, br s), 3.67 (2H, br s), 4.37 (2H, s), 6.39 (1H, s),  
7.57 (1H, dd, J=8.8, 2.0Hz), 7.78 (1H, dd, J=8.8, 2.0Hz), 7.88-  
7.95 (3H, m), 8.30 (1H, s).

MS (FD) m/z: 589 (M<sup>+</sup>, Cl<sup>35</sup>), 591 (M<sup>+</sup>, Cl<sup>37</sup>).

[Referential Example 342] 2-Aminomethyl-5-tert-  
20 butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

In tetrahydrofuran (100 ml), 5-tert-butoxycarbonyl-2-  
hydroxymethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine  
(WO94/21599) (2.10 g) was dissolved. After the addition of  
triphenylphosphine (2.66 g) and phthalimide (1.15 g),  
25 diethyl azodicarboxylate (1.28 ml) was added dropwise,  
followed by stirring at room temperature for 5 hours. The

reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby a colorless solid was obtained. The resulting solid was dissolved in ethanol (40 ml), followed by the addition of hydrazine hydrate (0.39 ml). The resulting mixture was heated under reflux for 5 hours. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 25:1), whereby the title compound (448 mg, 21%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.42 (9H, s), 2.72 (2H, m), 3.60 (2H, m), 3.80 (2H, s), 4.32 (2H, s), 6.64 (1H, s).

MS (FD)  $m/z$ : 268 $\text{M}^+$ .

[Referential Example 343] 1-[N-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]carbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (100 ml), 5-tert-butoxycarbonyl-2-aminomethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (150 mg) was dissolved. Under ice cooling, carbonyl diimidazole (136 mg) was added, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in toluene (50 ml). Under ice cooling,

triethylamine (0.23 ml) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (356 mg) were added, followed by stirring overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water and saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure and the residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 to 1:1), whereby the title compound (303 mg, 89%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.46(9H,s), 2.70(2H,br s), 3.07(4H,t,J=4.9Hz), 3.48(4H,t,J=4.9Hz), 3.66(2H,br s), 4.36(2H,br s), 4.39(2H,d,J=5.4Hz), 4.69(1H,t,J=5.4Hz), 6.58(1H,s), 7.58(1H,dd,J=8.8,2.0Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.87-7.93(3H,m), 8.30(1H,s).

MS (FD)  $m/z$ : 604 ( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 606 ( $\text{M}^+$ ,  $\text{Cl}^{37}$ ).

[Referential Example 344] 1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47(9H,s), 2.79(2H,br s), 3.12(4H,t,J=4.9Hz), 3.68(2H,br s), 3.84(4H,t,J=4.9Hz),

4.42 (2H, br s), 6.91 (1H, s), 7.59 (1H, dd, J=8.8, 2.0 Hz),  
7.75 (1H, dd, J=8.8, 2.0 Hz), 7.90-7.97 (3H, m), 8.30 (1H, s).

MS (FD) m/z: 575 ( $M^+$ ,  $Cl^{35}$ ), 577 ( $M^+$ ,  $Cl^{37}$ ).

[Referential Example 345] 1-[(5-tert-Butoxycarbonyl-  
5 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-  
[(6-chloronaphthalen-2-yl)sulfonyl]-2-  
ethoxycarbonylpiperazine

In the same manner as in Referential Example 319, the  
title compound was obtained using 5-tert-butoxycarbonyl-  
10 4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid  
(WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-  
ethoxycarbonylpiperazine (WO96/10022) as starting  
materials.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.32 (3H, t, J=7.3 Hz), 1.47 (9H, s), 2.35-  
15 2.46 (1H, m), 2.55-2.64 (1H, m), 2.80 (2H, br s), 3.15-  
3.20 (1H, m), 3.69 (2H, br s), 3.75-3.85 (1H, m),  
4.12 (2H, q, J=7.3 Hz), 4.20-4.36 (2H, m), 4.39-4.48 (3H, m),  
6.96 (1H, s), 7.59 (1H, dd, J=8.8, 2.0 Hz),  
7.75 (1H, dd, J=8.8, 2.0 Hz), 7.88-7.94 (3H, m), 8.32 (1H, s).

20 MS (FAB) m/z: 648 [ $(M+H)^+$ ,  $Cl^{35}$ ], 650 [ $(M+H)^+$ ,  $Cl^{37}$ ].

[Referential Example 346] 1-[(6-Chloronaphthalen-2-  
yl)sulfonyl]-4-[(5-cyano-4,5,6,7-tetrahydrothieno[3,2-  
c]pyridin-2-yl)carbonyl]piperazine

In ethanol, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-  
25 [(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
yl)carbonyl]piperazine hydrochloride (195 mg),



triethylamine (0.2 ml) and sodium acetate (118 mg) were suspended. Cyanogen bromide (114 mg) was added to the resulting suspension, followed by stirring at room temperature for 2 hours. To the residue obtained by concentration of the reaction mixture under reduced pressure, dichloromethane was added. The mixture was washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 100:1), whereby the title compound (51 mg, 28%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.93-2.98 (2H,m), 3.11-3.14 (4H,m), 3.49-3.55 (2H,m), 3.81-3.84 (4H,m), 4.29 (2H,s), 6.89 (1H,s), 7.59 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.75 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.90-7.94 (3H,m), 8.30 (1H,s).

MS (FAB)  $m/z$ : 501 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 503 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 347] 1-[N-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In benzene (10 ml), 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) (283 mg) was dissolved. To the resulting solution, triethylamine (0.14 ml) and diphenylphosphoryl azide (0.21 mg) were added, followed by heating under reflux for 2 hours. After the reaction mixture was cooled to room temperature, 1-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine hydrochloride (347 mg) and triethylamine (0.28 ml) were added and the mixture was heated under reflux overnight. After cooling to room temperature, to the reaction mixture was added  
 5 dichloromethane and a 3N aqueous sodium hydroxide solution. The resulting mixture was separated and aqueous layer was extracted with dichloromethane. The combined organic layer thus extracted was washed with 0.5N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and  
 10 saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 to 2:1), whereby the title compound (284 mg, 48%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45 (9H, s), 2.65 (2H, br s), 3.10 (4H, t, J=4.9Hz), 3.57 (4H, t, J=4.9Hz), 3.64 (2H, br s), 4.27 (2H, s), 6.15 (1H, br s), 7.58 (1H, dd, J=8.8, 2.0Hz), 7.73 (1H, dd, J=8.8, 2.0Hz), 7.87-7.93 (3H, m), 8.28 (1H, s).

20 MS (FAB) m/z: 591 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 593 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 348] 1-[N-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-N-methylcarbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

25 In N,N-dimethylformamide (10 ml), 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-

yl)carbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (147 mg) was dissolved. To the resulting solution, sodium hydride (60% in oil, 22 mg) was added, followed by stirring at room temperature for 30 minutes. After methyl iodide (0.023 ml) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 90 minutes, the residue obtained by the concentration of the reaction mixture under reduced pressure was added with ethyl acetate. The resulting mixture was washed with water and saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (43 mg) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49(9H,s), 2.63(2H,br s), 3.01(4H,t,J=4.9Hz), 3.13(3H,s), 3.40(4H,t,J=4.9Hz), 3.67(2H,br s), 4.31(2H,s), 6.21(1H,br s), 7.58(1H,dd,J=8.8,2.0Hz), 7.72(1H,dd,J=8.8,2.0Hz), 7.88-7.95(3H,m), 8.27(1H,s).

MS (FAB)  $m/z$ : 605  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 607  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 349] 1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained using 6-tert-butoxycarbonyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 (9H, s), 2.84 (2H, br s), 3.19 (4H, br),  
 3.72 (2H, t, J=5.4 Hz), 3.87 (2H, br s), 4.54 (2H, s), 4.63 (2H, br  
 s), 7.57 (1H, dd, J=8.8, 2.0 Hz), 7.76 (1H, dd, J=8.8, 2.0 Hz), 7.87-  
 7.94 (3H, m), 8.30 (1H, s).

MS (FAB) m/z: 577 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 579 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 350] 1-[(6-tert-Butoxycarbonyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-  
 [(6-chloronaphthalen-2-yl)sulfonyl]-2-  
 ethoxycarbonylpiperazine

In N,N-dimethylformamide (30 ml), 6-tert-  
 butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-  
 carboxylic acid (WO94/21599) (742 mg), 1-[(6-  
 chloronaphthalen-2-yl)sulfonyl]-3-ethoxycarbonylpiperazine  
 hydrochloride (WO96/10022) (1.00 g) and benzotriazol-1-  
 yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate  
 (PyBOP®) (1.50 g) were dissolved. Triethylamine (0.40 ml)  
 was added to the resulting solution, followed by stirring  
 overnight at room temperature. After the reaction mixture  
 was concentrated under reduced pressure, ethyl acetate was  
 added to the residue. The resulting mixture was washed  
 with water and saturated aqueous NaCl solution and then,  
 dried over anhydrous sodium sulfate. The residue obtained  
 by distilling off the solvent under reduced pressure was

purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (505 mg, 30%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.24-1.37 (3H,m), 1.47 (9H,s), 2.45-  
2.60 (1H,m), 2.62-2.71 (1H,m), 2.75-2.90 (2H,m), 3.65-  
3.94 (3H,m), 4.19-4.31 (2H,m), 4.45-4.72 (4H,m), 5.35 (1/2H,br s), 5.71-5.77 (1/2H,m), 6.72 (1H,br s),  
7.58 (1H,dd, J=8.8, 2.0Hz), 7.77 (1H,dd, J=8.8, 2.0Hz), 7.88-  
7.92 (3H,m), 8.33 (1H,s).

MS (FAB) m/z: 649 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 651 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 351] 1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (5 ml), 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine (487 mg) was dissolved. Methanol (5 ml) and a 1N aqueous sodium hydroxide solution (3 ml) were added to the resulting solution, followed by stirring at room temperature for 4 hours. After the reaction mixture was adjusted to pH 1 to 2 by the addition of 1N hydrochloric acid, ethyl acetate was added to separate the organic layer. After drying over anhydrous sodium sulfate, the residue obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (5 ml).

To the resulting solution, N-methylmorpholine (0.09 ml) and

isobutyl chloroformate (0.11 ml) were added dropwise at -20°C. After stirring at -20°C for 10 minutes, an ammonia-dichloromethane solution (0.50 ml) was added to the reaction mixture. The resulting mixture was stirred at -20°C for 10 minutes, followed by the addition of 1N aqueous hydrochloric acid solution in ethanol (10 ml). The reaction mixture was warmed up to room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in dichloroethane. The resulting solution was washed with 1N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), whereby the title compound (317 mg, 68%) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.41(9H,s), 2.39-2.86(4H,m), 3.60-3.80(4H,m), 4.25-4.34(1H,m), 4.36-4.34(1/2H,m), 4.62(2H,br s), 4.97(1/2H,br s), 5.44-5.52(1/2H,m), 6.19(1/2H,br s), 7.30-7.39(1H,m), 7.63-7.85(3H,m), 8.15(1H,d,J=8.8Hz), 8.20-8.29(2H,m), 8.48(1H,s).

MS (FAB) m/z: 620 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 622 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 352] 1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(E)-4-chlorostyrylsulfonyl]piperazine

In the same manner as in Referential Example 319, the

title compound was obtained using 6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as starting materials.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48 (9H, s), 2.87 (2H, br s), 3.31 (4H, m), 3.75 (2H, br s), 3.90 (2H, br s), 4.57 (2H, br s), 4.68 (2H, s), 6.64 (1H, d,  $J=15.6\text{Hz}$ ), 7.28-7.35 (5H, m).

MS (FAB)  $m/z$ : 553  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 555  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 353] (3S)-1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine  
10

In the same manner as in Referential Example 321, a reaction was effected using 5-tert-butoxycarbonyl-2-formyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (WO94/21599) and  
15 (3S)-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine trifluoroacetate as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49 (9H, s), 1.52-1.63 (1H, m), 2.03-2.12 (1H, m), 2.19-2.27 (1H, m), 2.35-2.54 (2H, m), 2.73-2.85 (3H, m), 3.59 (1H, d,  $J=13.9\text{Hz}$ ), 3.66 (1H, d,  $J=13.9\text{Hz}$ ),  
20 3.70 (2H, br s), 3.88-3.95 (1H, m), 4.39 (2H, s), 4.99 (1/2H, s), 5.02 (1/2H, s), 6.49 (1H, s), 7.55 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.82-7.90 (4H, m), 8.40 (1H, s).

MS (FD)  $m/z$ : 561 ( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 563 ( $\text{M}^+$ ,  $\text{Cl}^{37}$ ).

25 [Referential Example 354] (3S)-1-[(5-tert-Butoxycarbonyl-

4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-3-  
[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine

In the same manner as in Referential Example 319, the  
title compound was obtained using 5-tert-butoxycarbonyl-  
4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid  
(WO94/21599) and (3S)-3-[(6-chloronaphthalen-2-  
yl)sulfonamido]pyrrolidine trifluoroacetate as starting  
materials.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.50 (9H, s), 1.80-2.08 (2H, m), 2.75 (2H, br  
s), 3.48-3.87 (6H, m), 3.88-4.05 (1H, m), 4.37 (2H, br s),  
6.09 (1H, br s), 7.05-7.15 (1H, m), 7.55 (1H, dd, J=8.8, 1.5 Hz),  
7.79-7.91 (4H, m), 8.41 (1H, s).

MS (FAB) m/z: 576 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 578 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 355] (3S)-3-[[5-tert-Butoxycarbonyl-  
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methylamino]-  
1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In the same manner as in Referential Example 321, a  
reaction was effected using 5-tert-butoxycarbonyl-2-formyl-  
4,5,6,7-tetrahydrothieno[3,2-c]pyridine (WO94/21599) and  
(3S)-3-amino-1-[(6-chloronaphthalen-2-  
yl)sulfonyl]pyrrolidine as starting materials, whereby the  
title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48 (9H, s), 1.60-1.69 (1H, m), 1.95-  
2.05 (1H, m), 2.72 (2H, br s), 3.11 (1H, dd, J=10.3, 4.4 Hz), 3.30-  
3.46 (4H, m), 3.68 (2H, br s), 3.72 (2H, s), 4.36 (2H, s),  
6.44 (1H, s), 7.56 (1H, dd, J=8.8, 2.0 Hz), 7.86-7.91 (4H, m),



8.36(1H,s).

MS (FD) m/z: 561 ( $M^+$ ,  $Cl^{35}$ ), 563 ( $M^+$ ,  $Cl^{37}$ ).

[Referential Example 356] (3S)-3-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-  
5 1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In the same manner as in Referential Example 319, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and (3S)-3-amino-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine as starting materials.  
10

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.48(9H,s), 1.90-2.00(1H,m), 2.11-2.22(1H,m), 2.80(2H,br s), 3.32-3.42(1H,m), 3.44-3.57(3H,m), 3.71(2H,br s), 4.38(2H,d,J=1.5Hz), 4.40-4.49(1H,m), 5.80-5.87(1H,m), 6.96(1H,s),  
15 7.54(1H,dd,J=8.8,1.5Hz), 7.83-7.89(3H,m), 7.90(1H,d,J=8.8Hz), 8.37(1H,s).

MS (FAB) m/z: 576 [ $(M+H)^+$ ,  $Cl^{35}$ ], 578 [ $(M+H)^+$ ,  $Cl^{37}$ ].

[Referential Example 357] 1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-  
20 [(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine

In the same manner as in Referential Example 319, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride as starting  
25 materials.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47(9H,s), 2.01(2H,br s), 2.78(2H,br s),  
 3.37-3.54(4H,m), 3.68(2H,br s), 3.78(2H,t,J=6.1Hz),  
 3.86(2H,t,J=6.1Hz), 4.39(2H,s), 6.88(1H,br s),  
 7.55(1H,dd,J=8.8,2.0Hz), 7.75-7.80(1H,m), 7.83-7.90(3H,m),  
 8.33(1H,s).

MS (FD) m/z: 589 (M<sup>+</sup>, Cl<sup>35</sup>), 591 (M<sup>+</sup>, Cl<sup>37</sup>).

[Referential Example 358] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-cyanobenzofuran-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 319, a  
 reaction was effected using 6-cyanobenzofuran-2-carboxylic  
 acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
 hydrochloride as starting materials, whereby the title  
 compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.21(4H,s), 3.95(4H,s),  
 7.32(1H,d,J=1.0Hz), 7.55(1H,dd,J=8.3,1.0Hz),  
 7.59(1H,dd,J=8.8,2.0Hz), 7.72(1H,d,J=8.3Hz),  
 7.77(1H,dd,J=8.8,2.0Hz), 7.81(1H,s), 7.88-7.95(3H,m),  
 8.32(1H,s).

MS (FAB) m/z: 480 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 482 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 359] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyanobenzothiophen-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 319, a  
 reaction was effected using 5-cyanobenzothiophene-2-  
 carboxylic acid and 1-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.18(4H,s), 3.89(4H,s),  
7.43(1H,d,J=2.0Hz), 7.60(1H,d,J=8.8Hz), 7.73-7.80(2H,m),  
5 7.85-7.95(4H,m), 8.10(1H,s), 8.32(1H,s).

MS (FAB)  $m/z$ : 496  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 498  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 360] 6-Methoxy-3,4-dihydroisoquinoline

In tetrahydrofuran (100 ml), 3-methoxyphenethylamine  
10 (75.0 g) was dissolved. To the resulting solution, formic acid (60 ml) and acetic anhydride (108 ml) were added under ice cooling, followed by stirring overnight at room temperature. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture to separate  
15 the organic layer. The organic layer was washed with saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in benzene (200 ml), followed by the dropwise  
20 addition of phosphorus oxychloride (140 ml) under ice cooling. After stirring at  $70^\circ\text{C}$  for 15 minutes, the reaction mixture was successively added with ice and 2N hydrochloric acid. The resulting mixture was stirred for 1 hour under ice cooling. The water layer was separated from  
25 the reaction mixture, neutralized with potassium carbonate and then extracted with dichloromethane. The extract was

dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column

(dichloromethane ~ dichloromethane : methanol = 100:1),

5 whereby the title compound (13.5 g, 17%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.72 (2H, t,  $J=7.3\text{Hz}$ ), 3.72 (2H, t,  $J=7.3\text{Hz}$ ), 3.83 (3H, s), 6.68 (1H, d,  $J=2.4\text{Hz}$ ), 6.79 (1H, dd,  $J=8.3, 2.4\text{Hz}$ ), 7.22 (1H, d,  $J=8.3\text{Hz}$ ), 8.25 (1H, s).

MS (FAB)  $m/z$ : 162 ( $\text{M}+\text{H}$ ) $^+$ .

10 [Referential Example 361] 6-Methoxy-1,2,3,4-tetrahydroisoquinoline

In methanol (100 ml), 6-methoxy-3,4-dihydroisoquinoline (10.4 g) was dissolved. To the resulting solution, water (10 ml) and then sodium  
15 borohydride (6.10 g) were added. The resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane, followed by washing with water. The organic layer thus separated was  
20 dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column

(dichloromethane ~ dichloromethane : methanol = 100:15),

whereby the title compound (7.95 g, 76%) was obtained.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.79 (2H, t,  $J=5.9\text{Hz}$ ), 3.12 (2H, t,  $J=5.9\text{Hz}$ ),

3.76(3H,s), 3.96(2H,s), 6.62(1H,s),  
6.70(1H,dd,J=8.3,2.4Hz), 6.92(1H,d,J=8.3Hz).

MS (FAB) m/z: 164 (M+H)<sup>+</sup>.

[Referential Example 362] 6-Hydroxy-1,2,3,4-

5 tetrahydroisoquinoline hydrochloride

In dimethyl sulfide (20 ml), 6-methoxy-1,2,3,4-tetrahydroisoquinoline (7.75 g) was dissolved. Under ice cooling, aluminum chloride (19.0 g) was added to the resulting solution, followed by stirring at room  
10 temperature for 3 hours. Dichloromethane and dilute hydrochloric acid were added to separate the water layer. The water layer was made basic by the addition of a saturated aqueous solution of sodium bicarbonate, followed by extraction with dichloromethane. The extract was dried  
15 over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in saturated solution of hydrochloride in ethanol (100 ml). To the residue obtained by distilling off the solvent under reduced pressure, ethyl acetate was added. The solid thus  
20 precipitated was collected by filtration, whereby the title compound (7.91 g, 90%) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.06(2H,t,J=5.9Hz), 3.43(2H,m),  
4.25(2H,s), 6.76(1H,d,J=2.0Hz), 6.83(1H,dd,J=8.3,2.0Hz),  
7.15(1H,d,J=8.3Hz), 9.71(3H,br s).

25 MS (FAB) m/z: 150 (M+H)<sup>+</sup>.

[Referential Example 363] 2-tert-Butoxycarbonyl-6-hydroxy-

## 1,2,3,4-tetrahydroisoquinoline

In methanol (100 ml), 6-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (7.87 g) was dissolved. To the resulting solution, triethylamine (4.67 ml) and di-tert-butyl dicarbonate (13.95 g) were added, followed by stirring at room temperature for 3 hours. Ethyl acetate was added to the residue obtained by concentration of the reaction mixture under reduced pressure. The resulting mixture was washed with 1N hydrochloric acid, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 10:1 to 3:1), whereby the title compound (9.96 g, 94%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.49(9H,s), 2.75(2H,t,J=5.9Hz), 3.61(2H,t,J=5.9Hz), 4.48(2H,s), 6.25(1H,br s), 6.64(1H,d,J=2.4Hz), 6.70(1H,br s), 6.93(1H,d,J=7.8Hz).

[Referential Example 364] 2-tert-Butoxycarbonyl-6-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydroisoquinoline

In pyridine (100 ml), 2-tert-butoxycarbonyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (9.96 g) was dissolved. To the resulting solution, trifluorosulfonic anhydride (8.10 ml) was added dropwise under ice cooling, followed by stirring at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography on a silica gel

column (hexane : ethyl acetate = 10:1 to 6:1), whereby the title compound (13.47 g, 88%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49(9H,s), 2.87(2H,t,J=5.9Hz),

5 3.66(2H,t,J=5.9Hz), 4.59(2H,s), 7.06(1H,br s),

7.08(1H,d,J=8.3Hz), 7.17(1H,d,J=8.3Hz).

Elementary analysis for  $\text{C}_{15}\text{H}_{18}\text{F}_3\text{NO}_5\text{S}$

Calculated: C, 47.24; H, 4.76; F, 14.94; N, 3.67; S, 8.41.

Found: C, 47.34; H, 4.72; F, 15.25; N, 3.42; S, 8.65.

10 [Referential Example 365] 2-tert-Butoxycarbonyl-6-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline

In methanol (50 ml), 2-tert-butoxycarbonyl-6-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydroisoquinoline (1.34 g) was dissolved, followed by the addition of

15 triethylamine (0.73 ml), palladium (II) acetate (40 mg) and 1,3-(diphenylphosphino)propane (145 mg). Under a carbon monoxide gas stream, the resulting mixture was stirred

overnight at 70°C. The reaction mixture was concentrated under reduce pressure and the residue was purified by

20 chromatography on a silica gel column (hexane : ethyl acetate = 15:1), whereby the title compound (665 mg, 65%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50(9H,s), 2.88(2H,m), 3.66(2H,br s),

3.91(3H,s), 4.62(2H,s), 7.17(1H,d,J=7.8Hz), 7.83(1H,s),

25 7.84(1H,d,J=7.8Hz).

[Referential Example 366] 1-[(2-tert-Butoxycarbonyl-

1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained using 2-tert-butoxycarbonyl-6-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48 (9H, s), 2.76 (2H, t, J=5.4 Hz), 3.09 (4H, br), 3.60 (2H, t, J=5.4 Hz), 3.77 (4H, br), 4.52 (2H, s), 7.12-7.25 (3H, m), 7.59 (1H, dd, J=8.8, 2.0 Hz), 7.75 (1H, dd, J=8.8, 2.0 Hz), 7.88-7.95 (3H, m), 8.30 (1H, s).

MS (FAB) m/z: 570 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 572 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 367] 1-tert-Butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine

In methanol (1000 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[ethoxycarbonyl]piperazine hydrochloride (W096/10022) (43.0 g) was dissolved, followed by the addition of triethylamine (17.1 ml) and di-tert-butyl dicarbonate (27.0 g). The resulting mixture was stirred at room temperature for 3 hours. The residue obtained by concentration of the reaction mixture under reduced pressure was added with ethyl acetate and the resulting mixture was washed with 1N hydrochloric acid. The organic layer thus extracted was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by



chromatography on a silica gel column (hexane : ethyl acetate = 8:1), whereby the title compound (46.0 g, 93%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.24-1.32 (3H,m), 1.33-1.50 (9H,m),  
 2.37 (1H,m), 2.54 (1H,d,J=10.7Hz), 3.15-3.41 (1H,m), 3.68-  
 4.08 (2H,m), 4.10-4.39 (3H,m), 4.62 (1/2H,br s), 4.82 (1/2H,br  
 s), 7.58 (1H,dd,J=8.8,2.0Hz), 7.75 (1H,dd,J=8.8,2.0Hz), 7.87-  
 7.94 (3H,m), 8.31 (1H,d,J=2.0Hz).

MS (FAB)  $m/z$ : 483 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 485 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

Elementary analysis for  $\text{C}_{22}\text{H}_{27}\text{ClNO}_6\text{S}$

Calculated: C, 54.71; H, 5.63; Cl, 7.34; N, 5.80; S, 6.64.

Found: C, 54.89; H, 5.42; Cl, 7.15; N, 5.76; S, 6.24.

[Referential Example 368] 1-tert-Butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid

In tetrahydrofuran (40 ml), 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine (23.0 g) was dissolved, followed by the addition of ethanol (40 ml) and a 3N aqueous sodium hydroxide solution (30 ml). The resulting mixture was stirred at room temperature for 3 hours. To the reaction mixture, 1N hydrochloric acid was added to make it acidic and then ethyl acetate was added to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate. The solid precipitated by distilling off the solvent under reduced pressure was collected by filtration, whereby the title compound (23.8 g, quant.) was obtained as

a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.41(1H,m), 2.59(1H,m), 3.15-3.38(1H,m),  
3.70-4.08(2H,m), 4.20-4.39(1H,m), 4.72(1/2H,br s),  
4.91(1/2H,br s), 7.58(1H,dd,J=8.8,J=2.0Hz),  
5 7.76(1H,dd,J=8.8,2.0Hz), 7.87-7.95(3H,m), 8.34(1H,s).

Mass (FAB)  $m/z$ : 455( $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 457( $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

Elementary analysis for  $\text{C}_{20}\text{H}_{23}\text{ClNO}_6\text{S}$

Calculated: C, 52.80; H, 5.10; Cl, 7.79; N, 6.16; S, 7.05.

Found: C, 52.62; H, 5.00; Cl, 7.75; N, 6.22; S, 6.83.

10 [Referential Example 369] 1-tert-Butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 367 or  
368, the title compound was obtained using 1-[(6-  
15 chloronaphthalen-2-yl)sulfonyl]-3-

[methoxycarbonylmethyl]piperazine as a starting material.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.38(9H,s), 2.32(1H,dt,J=12.2,3.4Hz),  
2.48(1H,dd,J=12.2,3.4Hz), 2.61(1H,dd,J=15.6,5.9Hz),  
2.86(1H,dd,J=15.6,8.3Hz), 3.13(1H,s), 3.68(3H,s), 3.74-  
20 4.08(3H,m), 7.58(1H,dd,J=8.8,2.0Hz),  
7.74(1H,dd,J=8.8,2.0Hz), 7.89-7.94(3H,m), 8.29(1H,s).

MS (FAB)  $m/z$ : 469 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 471 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

Elementary analysis for  $\text{C}_{22}\text{H}_{27}\text{ClN}_2\text{O}_7\text{S}$

Calculated: C, 54.71; H, 5.63; Cl, 7.34; N, 5.80; S, 6.64.

25 Found: C, 54.74; H, 5.69; Cl, 7.34; N, 5.84; S, 6.62.

[Referential Example 370] 6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

In anhydrous tetrahydrofuran (500 ml), 6-ethoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (WO94/21599) (21.0 g) was dissolved, followed by the addition of a solution of lithium aluminum hydride in tetrahydrofuran (a 1.0M solution, 200 ml) under ice cooling. The resulting mixture was stirred at room temperature for 2 hours. Water (7 ml) was then added slowly to the reaction mixture. After the termination of the reaction, a 1N aqueous potassium hydroxide solution (7 ml) and anhydrous magnesium sulfate were successively added. After removal of the insoluble matter by filtration, the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by distillation under reduced pressure (1.5 mmHg, boiling point: 82 to 85°C), whereby the title compound (6.10 g, 40%) was obtained as a colorless oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.52(3H,s), 2.83(2H,t,J=5.9Hz), 2.98(2H,t,J=5.9Hz), 3.70(2H,s), 3.87(2H,br s), 8.63(1H,s).  
MS (FAB)  $m/z$ : 155  $[(\text{M}+\text{H})^+]$ .

[Referential Example 371] Lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate

In anhydrous tetrahydrofuran (200 ml), 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (6.43 g) was dissolved, followed by the dropwise addition of a solution

(1.47M, 34.00 ml) of n-butyl lithium in n-hexane at an external temperature of  $-78^{\circ}\text{C}$ . The resulting mixture was stirred for 40 minutes without changing the temperature. Then a carbon dioxide gas was blown into the reaction mixture for 1 hour. After warming up to room temperature, the reaction mixture was concentrated under reduced pressure, whereby the title compound (9.42 g, quant.) was obtained as a pale brown foamy solid.

$^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 2.37(3H,s), 2.64-2.77(4H,m),  
3.54(2H,s).

MS (FAB)  $m/z$ : 199 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 372] N-[[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]glycine ethyl ester trifluoroacetate

In the same manner as in Referential Example 319, an amide bond was formed using 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid as a starting material, followed by deprotection using trifluoroacetic acid, whereby the title compound was obtained.

$^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 1.20(3H,t, $J=7.3\text{Hz}$ ), 2.47-2.82(2H,m),  
3.14-3.28(1H,m), 3.30-3.39(1H,m), 3.72-3.79(1H,m),  
3.95(2H,d, $J=5.9\text{Hz}$ ), 4.08-4.18(3H,m),  
4.20(1H,dd, $J=11.2, 3.4\text{Hz}$ ), 7.75(1H,dd, $J=8.8, 2.0\text{Hz}$ ),  
7.84(1H,d, $J=8.8\text{Hz}$ ), 8.23(1H,d, $J=8.8\text{Hz}$ ), 8.28(1H,s),  
8.30(1H,d, $J=8.8\text{Hz}$ ), 8.55(1H,s), 9.29(1H,t, $J=5.9\text{Hz}$ ).

MS (FAB) m/z: 440 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 442 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 373] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(morpholin-4-yl)carbonyl]methyl]piperazine hydrochloride

5 In the same manner as in Referential Example 319, an amid bond was formed using 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine and morpholine as starting materials, followed by deprotection In the same manner as  
10 in Referential Example 1, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.65-2.91(4H,m), 3.10-3.22(1H,m), 3.30-3.82(12H,m), 7.74(1H,d,J=8.8Hz), 7.84(1H,d,J=8.8Hz), 8.20(1H,d,J=8.8Hz), 8.22-8.31(2H,m), 8.55(1H,s), 9.18(1H,br  
15 s), 9.32(1H,br s).

MS (FAB) m/z: 438 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 440 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 374] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[N-(morpholin-4-yl)carbamoyl]piperazine trifluoroacetate

20 In the same manner as in Referential Example 372, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> at 100°C) δ: 2.59-3.97(13H,m), 4.00-4.12(1H,m), 4.38-4.50(1H,m), 7.68(1H,dd,J=8.8,2.4Hz), 7.84(1H,d,J=8.8Hz), 8.15(1H,d,J=8.8Hz), 8.18(1H,s),  
25 8.22(1H,d,J=8.8Hz), 8.48(1H,s), 9.18(1H,br s).

MS (FAB)  $m/z$ : 439  $[(M+H)^+, Cl^{35}]$ , 441  $[(M+H)^+, Cl^{37}]$ .

[Referential Example 375] Ethyl N'-[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]hydrazinoacetate hydrochloride

5 In the same manner as in Referential Example 372, the title compound was obtained.

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.20-1.24 (3H,m), 2.55-2.90 (2H,m), 3.00-3.20 (1H,m), 3.30-3.38 (1H,m), 3.53-3.87 (3H,m), 3.94-4.19 (3H,m), 4.27 (1/2H,d,J=9.8Hz), 4.54-4.63 (1/2H,m),  
10 4.95 (1H,br s), 7.75 (1H,dd,J=8.8,2.0Hz), 7.84-7.95 (1H,m), 8.19-8.32 (3H,m), 8.56 (1H,s), 8.80-9.00 (1H,m), 9.78-10.20 (1H,m).

MS (FAB)  $m/z$ : 455  $[(M+H)^+, Cl^{35}]$ , 457  $[(M+H)^+, Cl^{37}]$ .

[Referential Example 376] 4-(Aminoacetyl)morpholine  
15 hydrochloride

In N,N-dimethylformamide (100 ml), N-tert-butoxycarbonylglycine (2.00 g), morpholine (1.00 ml), 1-hydroxybenzotriazole monohydrate (1.74 g) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
20 (2.84 g) were dissolved, followed by stirring overnight at room temperature. After concentration under reduced pressure, the residue was diluted with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under  
25 reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 100:1), whereby a

colorless foam was obtained. The substance was dissolved in dichloromethane (2 ml), followed by the addition of saturated solution of hydrochloride in ethanol (10 ml). The resulting mixture was stirred at room temperature for 5 minutes. The reaction mixture was concentrated to dryness under reduced pressure, whereby the title compound (1.80 g, quant.) was obtained as a pale yellow foam was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.39(2H,t,J=4.5Hz), 3.48(2H,t,J=4.5Hz), 3.52-3.63(4H,m), 3.77-3.90(2H,m), 8.32(3H,br s).

MS (FAB)  $m/z$ : 145 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 377] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[N-[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine hydrochloride

In the same manner as in Referential Example 372, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.67(1H,d,J=11.2Hz), 2.79(1H,d,J=11.2Hz), 3.09-3.18(1H,m), 3.17-3.30(1H,m), 3.42(1H,d,J=13.2Hz), 3.45-3.74(8H,m), 3.82(1H,d,J=12.2Hz), 4.10-4.30(4H,m), 7.86(1H,d,J=8.8Hz), 7.95(1H,d,J=8.8Hz), 8.32(1H,d,J=8.8Hz), 8.40(1H,s), 8.41(1H,d,J=8.8Hz), 8.67(1H,d,J=8.8Hz), 8.93(1H,br s), 9.12(1H,d,J=4.9Hz), 10.03(1H,br s).

MS (FAB)  $m/z$ : 481 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 483 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 378] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

trifluoroacetate

In the same manner as in Referential Example 319, 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine-2-carboxylic acid was reacted with methylamine to form an amide bond and then the protecting group was removed using trifluoroacetic acid, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.54-2.65 (2H, m), 2.67 (3H, d, J=3.9 Hz), 3.12-3.22 (1H, m), 3.33 (1H, d, J=13.2 Hz), 3.70 (1H, d, J=12.2 Hz), 4.04 (2H, d, J=8.8 Hz), 7.75 (1H, dd, J=8.8, 2.0 Hz), 7.87 (1H, d, J=8.8 Hz), 8.20 (1H, d, J=8.8 Hz), 8.27 (1H, s), 8.29 (1H, d, J=8.8 Hz), 8.58 (1H, s), 8.70 (1H, d, J=4.4 Hz), 9.06 (1H, br s).

MS (FAB) m/z: 440 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 442 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

In the same manner as in Referential Example 378, Compounds of Referential Examples 379 to 384 were synthesized.

[Referential Example 379] 4-[[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]morpholine

trifluoroacetate

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.49-2.58 (1H, m), 2.64-2.75 (1H, m), 3.09-3.81 (11H, m), 3.93 (1H, d, J=12.2 Hz), 4.76 (1H, dd, J=10.7, 2.4 Hz), 7.75 (1H, d, J=8.8 Hz), 7.90 (1H, d, J=8.8 Hz), 8.21 (1H, d, J=8.8 Hz), 8.27 (1H, s), 8.29 (1H, d, J=8.8 Hz), 8.58 (1H, s), 9.15 (1H, br s).

MS (FAB) m/z: 440 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 442 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].



[Referential Example 380] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(N-tert-butoxy)carbonyl]piperazine trifluoroacetate

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.58-2.70 (2H,m), 3.14-3.23 (1H,m), 3.30-3.40 (1H,m), 3.64 (1H,d,J=12.2Hz), 3.97 (1H,d,J=12.2Hz), 4.05 (1H,dd,J=10.2,3.4Hz), 7.74 (1H,dd,J=8.8,2.0Hz), 7.87 (1H,d,J=8.8Hz), 8.21 (1H,d,J=8.8Hz), 8.27 (1H,d,J=2.0Hz), 8.29 (1H,d,J=8.8Hz), 8.57 (1H,s), 11.24 (1H,s).

MS (FAB) m/z: 426 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 428 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 [Referential Example 381] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[(N-isopropyl)carbamoyl]piperazine hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.05-1.18 (6H,m), 2.60-2.77 (2H,m), 3.08-3.16 (1H,m), 3.30-3.41 (1H,m), 3.67 (1H,d,J=12.2Hz), 3.80-3.90 (1H,m), 4.99 (2H,d,J=7.8Hz), 7.74 (1H,dd,J=8.8,2.0Hz), 7.87 (1H,dd,J=8.8,1.5Hz), 8.22 (1H,d,J=8.8Hz), 8.28 (1H,s), 8.31 (1H,d,J=8.8Hz), 8.58 (1H,s), 8.74 (1H,d,J=7.3Hz).

MS (FAB) m/z: 396 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 398 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Referential Example 382] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[piperidin-1-yl]carbonyl]methyl]piperazine hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.45-1.90 (8H,m), 2.78 (1H,d,J=16.1Hz), 3.08-3.20 (1H,m), 3.20-3.60 (7H,m), 3.68-3.92 (3H,m), 7.58 (1H,d,J=8.8Hz), 7.71 (1H,d,J=8.8Hz), 7.85-7.98 (3H,m), 8.31 (1H,s), 9.09 (1H,br s), 11.32 (1H,br s).

25

MS (FAB) m/z: 436 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 438 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 383] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[N-(2-methoxybenzyl)]carbamoyl]piperazine hydrochloride

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.69(1H,t,J=11.2Hz), 2.72-2.30(1H,m),  
3.08-3.16(1H,m), 3.31-3.37(1H,m), 3.68(1H,d,J=12.2Hz),  
4.05(1H,d,J=12.2Hz), 4.14(1H,dd,J=10.3,3.4Hz),  
4.29(1H,d,J=5.4Hz), 6.93(1H,t,J=7.3Hz), 7.02(1H,d,J=7.8Hz),  
7.24(1H,d,J=7.3Hz), 7.29(1H,t,J=7.8Hz),  
10 7.77(1H,dd,J=8.8,2.0Hz), 7.88(1H,d,J=8.8Hz),  
8.23(1H,d,J=8.8Hz), 8.30(1H,s), 8.32(1H,d,J=8.8Hz),  
8.59(1H,s), 9.17(1H,t,J=5.4Hz).

MS (FAB) m/z: 474 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 476 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 384] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)]carbamoyl]piperazine

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.54-2.75(2H,m), 3.02-3.51(7H,m),  
3.70(1H,d,J=12.2Hz), 7.75(1H,d,J=8.8Hz),  
7.87(1H,d,J=8.8Hz), 8.22(1H,d,J=8.8Hz), 8.28(1H,s),  
8.31(1H,d,J=8.8Hz), 8.58(1H,s), 8.97(1H,t,J=5.4Hz),  
20 10.01(1H,br s).

MS (FAB) m/z: 412 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 414 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 385] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[carbamoylmethyl]piperazine hydrochloride

In N,N-dimethylformamide (20 ml), 1-tert-  
25 butoxycarbonyl-2-carboxymethyl-4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine (800 mg) was dissolved, followed by the addition of pyridine (0.85 ml), ammonium bicarbonate (417 mg) and di-tert-butoxy carbonate (1.15 g). The resulting mixture was stirred at room temperature for 7 hours. After concentration of the reaction mixture under reduced pressure, the residue was added with dichloromethane, washed with 1N hydrochloric acid and a saturated aqueous solution of sodium bicarbonate, each once and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. After the addition of saturated aqueous hydrochloric acid in ethanol (30 ml) to the residue, the resulting mixture was concentrated under reduced pressure. While washing with ethanol, the solid thus precipitated was removed by filtration. The filtrate was then concentrated under reduced pressure. The residue was crystallized in methanol, whereby the title compound (426 mg) was obtained as a colorless solid.

IR(KBr)cm<sup>-1</sup>: 3185, 2917, 2684, 2607, 1677, 1342, 1299, 1170, 1155, 1135, 755, 692, 578.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.58-2.65(1H,m), 2.72-2.83(1H,m), 3.12-3.21(1H,m), 3.30-3.48(3H,m), 3.55-3.81(1H,m), 7.21(1H,br s), 7.66(1H,br s), 7.73(1H,dd,J=8.8,2.0Hz), 7.85(1H,d,J=8.8Hz), 8.20(1H,d,J=8.8Hz), 8.26(1H,s), 8.29(1H,d,J=8.8Hz), 8.56(1H,s), 9.02-9.23(2H,m).

MS (FAB) m/z: 368 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 370 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 386] 1-(3-Furyl)-2-nitroethylene

To a solution of 3-furaldehyde (10.0 g) in ethanol (200 ml), nitromethane (6.37 g) was added at room temperature, followed by the dropwise addition of a 10N-  
5 aqueous sodium hydroxide solution (11.0 ml) at 0°C. The resulting mixture was stirred for 1 hour. The reaction mixture was poured into a 15% aqueous solution of hydrochloric acid (500 ml). The precipitate so formed was collected by filtration and dried, whereby the title  
10 compound (8.01 g) was obtained as a yellowish white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 6.57(1H,d,J=2.0Hz), 7.39(1H,d,J=13.4Hz), 7.52(1H,br s), 7.83(1H,br s), 7.94(1H,d,J=13.4Hz).

[Referential Example 387] 2-(t-Butoxycarbonylamino)-1-(3-furyl)ethane

15 In tetrahydrofuran (170 ml), lithium aluminum hydride (2.20 g) was suspended, followed by the dropwise addition of a solution of 1-(3-furyl)-3-nitroethylene (8.00 g) in tetrahydrofuran (80 ml) at room temperature over 2 hours. The resulting mixture was stirred for 30 minutes. After  
20 the reaction mixture was cooled to 0°C, ethyl acetate (50 ml) and then water (10 ml) were dropwise added thereto. The mixture was stirred while gradually warmed up. The reaction mixture was subjected to Celite filtration by using ethyl acetate. After the filtrate was concentrated,  
25 the residue was dissolved in methylene chloride (200 ml). Di-t-butyl dicarbonate (12.6 g) was added to the resulting

solution at room temperature and the mixture was stirred for 1 hour. The reaction mixture was concentrated and the residue was purified by chromatography on a silica gel column (400 g of silica gel, hexane : ethyl acetate = 15:1 → 8:1), whereby the title compound (4.30 g) was obtained as a pale yellow transparent oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.44(9H,s), 2.61(2H,t,J=6.8Hz), 3.25-3.37(2H,m), 4.57(1H,br s), 6.29(1H,s), 7.26(1H,s), 7.37(1H,s).

[Referential Example 388] 6-(t-Butoxycarbonyl)-4,5,6,7-tetrahydrofuro[2,3-c]pyridine

Paraformaldehyde (625 mg) and p-toluenesulfonic acid (49.5 mg) were added to a solution of 2-(t-butoxycarbonylamino)-1-(3-furyl)ethane (2.20 g) in toluene (300 ml), followed by heating under reflux for 2 hours while dehydrating using a Dean Stark apparatus. After the reaction mixture was allowed to cool down to room temperature, a saturated aqueous solution (200 ml) of sodium bicarbonate and ethyl acetate (200 ml) were added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (100 g of silica gel, hexane : ethyl acetate = 15:1 → 10:1), whereby

the title compound (1.04 g) was obtained as a white solid.

IR(KBr)  $\text{cm}^{-1}$ :

3145, 3005, 2976, 2925, 2862, 1695, 1448, 1419, 1365, 1279,  
1228, 1165, 1124, 912, 895, 758.

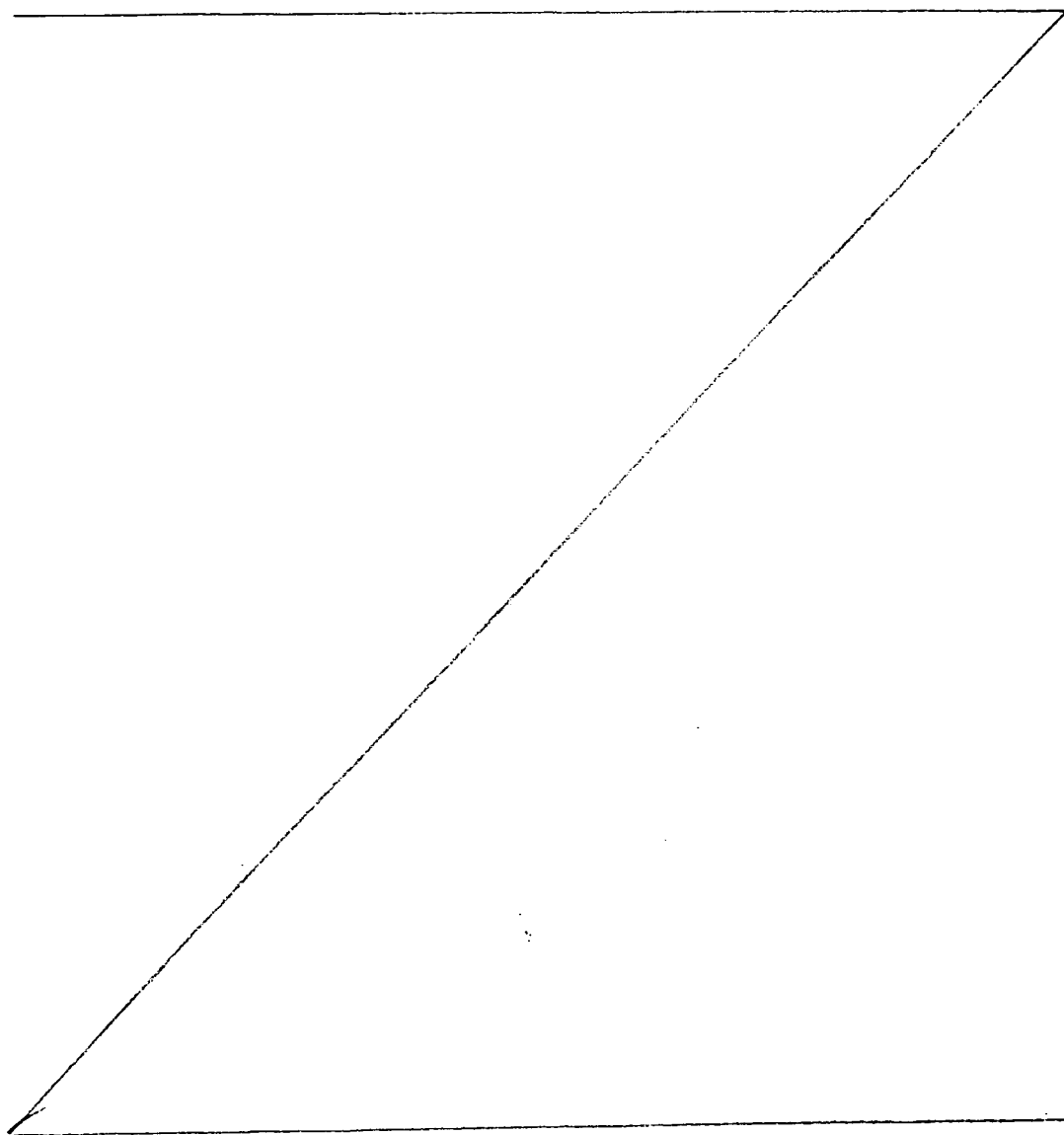
5  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.48(9H,s), 2.52(2H,br s), 3.63(2H,br s),  
4.44(2H,s), 6.25(1H,s), 7.29(1H,s).

MS (FAB)  $m/z$ : 224  $[(\text{M}+\text{H})^+]$ , 168  $[(\text{M}+\text{H}-\text{isobutene}(56))^+]$ .

[Referential Example 389] 6-Methyl-4,5,6,7-  
tetrahydrofuro[2,3-c]pyridine

10 To 6-(*t*-butoxycarbonyl)-4,5,6,7-tetrahydrofuro[2,3-  
c]pyridine (1.05 g), a saturated solution of hydrochloride  
in ethanol (30 ml) was added at room temperature. After  
stirring for 2 hours, the reaction mixture was  
concentrated. The residue thus obtained was suspended in  
15 methylene chloride (20 ml), followed by the addition of  
methanol (20 ml), triethylamine (1.31 ml), acetic acid (810  
 $\mu\text{l}$ ), formaldehyde (a 37% aqueous solution, 610  $\mu\text{l}$ ) and  
sodium triacetoxyborohydride (1.51 g) at room temperature.  
The resulting mixture was stirred for 1 hour. To the  
20 reaction mixture, a saturated aqueous solution (100 ml) of  
sodium bicarbonate and methylene chloride (20 ml) were  
added to cause separation. The water layer was extracted  
with methylene chloride (3 x 10 ml). The organic layers  
were combined, dried over anhydrous sodium sulfate and  
25 concentrated under reduced pressure. The residue thus

obtained was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : acetone = 1:1 → 1:2 → methylene chloride : methanol = 10:1), whereby the title compound (434 mg) was obtained as a  
5 colorless transparent oil.



$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.48 (3H, s), 2.56 (2H, t,  $J=5.6\text{Hz}$ ),  
2.67 (2H, t,  $J=5.6\text{Hz}$ ), 3.48 (2H, s), 6.23 (1H, d,  $J=2.0\text{Hz}$ ),  
7.25 (1H, s).

[Referential Example 390] 3-Aminoacrylaldehyde

5           To a solution of isoxazole (5.00 g) in methanol (100  
ml), Raney nickel ("R-100", product of Nikko Chemical)  
(about 1.0 g) was added at room temperature. Under a  
hydrogen atmosphere (3.05 - 2.65  $\text{kg/cm}^2$ ), the resulting  
mixture was stirred for 3 hours. The reaction mixture was  
10 subjected to Celite filtration and the filtrate was  
concentrated. The residue thus obtained was reprecipitated  
in a chloroform - hexane system, whereby the title compound  
(4.91 g, 69.1 mmol, 95%) was obtained as a yellow solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.60-5.20 (2H, br),  
15 5.45 (1H, dd,  $J=12.7, 8.3\text{Hz}$ ), 7.15 (1H, d,  $J=12.7\text{Hz}$ ),  
9.18 (1H, d,  $J=8.3\text{Hz}$ ).

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$ : 5.55 (1H, dd,  $J=12.2, 9.3\text{Hz}$ ),  
7.59 (1H, d,  $J=12.2\text{Hz}$ ), 8.98 (1H, d,  $J=9.3\text{Hz}$ ).

[Referential Example 391] 6-(t-Butoxycarbonyl)-5,6,7,8-  
20 tetrahydro-1,6-naphthylidine

Triethylamine (1.50 ml) and pyridinium acetate (30.0  
mg) were added to 1-benzyl-4-piperidone (3.80 g) and 3-  
aminoacrylaldehyde (2.10 g), followed by stirring under  
heat at  $120^\circ\text{C}$ . After 22 hours, the reaction mixture was  
25 allowed to cool down to room temperature and the brown



caramel-like substance thus obtained was dissolved in a 3N aqueous solution of hydrochloric acid. The resulting solution was extracted with chloroform (2 x 50 ml). To the water layer, a saturated aqueous solution (50 ml) of sodium bicarbonate was added, followed by extraction with chloroform (3 x 60 ml). The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was distilled (0.90 mmHg, 145 to 150°C), whereby about 3:2 mixture (1.98 g) of 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthylidene in the form of a pale yellow transparent oil and 1-benzyl-4-piperidone as the starting material was obtained.

The mixture was dissolved in acetic acid (25 ml). To the resulting solution, 10% palladium-carbon (500 mg) was added, followed by vigorous stirring at 50 to 60°C under a hydrogen atmosphere (about 1 atm). After the stirring was continued for 2 hours, the reaction mixture was allowed to cool down and filtered. By the concentration of the filtrate, a residue containing 5,6,7,8-tetrahydro-1,6-naphthylidene in the form of a colorless transparent oil was obtained.

The residue was dissolved in toluene (20 ml), followed by the addition of a 40% aqueous solution of sodium hydroxide (30 ml) and di-*t*-butyl dicarbonate (3.20 g, 14.7 mmol) at room temperature. After stirring for 10 minutes, water (30 ml) and toluene (20 ml) were added to the

reaction mixture to cause separation. The water layer was extracted with toluene (30 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (50 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : ethyl acetate = 5:1 → 3:1), whereby the title compound (981 mg) was obtained as a colorless transparent oil.

IR(KBr)cm<sup>-1</sup>: 2974, 1693, 1577, 1454, 1419, 1392, 1365, 1288, 1259, 1241, 1228, 1161, 1119, 1097, 989, 930, 881, 862, 789, 768, 737.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.50(9H,s), 3.01(2H,t,J=5.9Hz), 3.76(2H,t,J=5.9Hz), 4.59(2H,s), 7.13(1H,dd,J=7.8,4.9Hz), 7.41(1H,d,J=7.8Hz), 8.43(1H,d,J=4.9Hz).

MS (FAB) m/z: 235 [(M+H)<sup>+</sup>], 179 [(M+H)<sup>+</sup>-isobutene(56)].

[Referential Example 392] 6-(t-Butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidin-1-oxide

To a solution of 6-(t-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidine (1.72 g) in methylene chloride (40 ml), metachloroperbenzoic acid (3.80 g) was added at 0°C and the resulting mixture was stirred. Thirty minutes later, dimethyl sulfide (1.62 ml) was added to the reaction mixture, followed by stirring at room temperature for 30 minutes. To the reaction mixture, a saturated aqueous

solution (150 ml) of sodium bicarbonate and methylene chloride (30 ml) were added to cause separation. The water layer was extracted with methylene chloride (3 x 30 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column (100 g of silica gel, methylene chloride : methanol = 20:1 → 10:1), whereby the title compound (1.80 g, 7.19 mmol, 98%) was obtained as a colorless transparent oil.

IR(KBr)cm<sup>-1</sup>: 2976, 2929, 2860, 1697, 1431, 1365, 1263, 1240, 1167, 1115, 1028, 910, 771.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.49(9H,s), 3.05(2H,t,J=5.9Hz), 3.75(2H,t,J=5.9Hz), 4.59(2H,s), 7.04(1H,d,J=8.8Hz), 7.14(1H,dd,J=8.8,5.9Hz), 8.18(1H,d,J=5.9Hz).

[Referential Example 393] 6-(t-Butoxycarbonyl)-2-cyano-5,6,7,8-tetrahydro-1,6-naphthylidene

To a solution of 6-(t-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-naphthylidin-1-oxide (760 mg) in methylene chloride (15 ml), trimethylsilyl cyanide (610 μl) was added at room temperature and the resulting mixture was stirred for 5 minutes. To the reaction mixture, N,N-dimethylcarbamoyl chloride (420 μl) was added, followed by stirring for 41 hours. To the reaction mixture, a saturated aqueous solution (50 ml) of sodium bicarbonate

and chloroform (30 ml) were added to cause separation. The water layer was extracted with chloroform (30 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column (50 g of silica gel, methylene chloride : ethyl acetate = 6:1 → 2:1), whereby the title compound (697 mg) was obtained as a white solid. The resulting white solid was recrystallized from a hexane - methylene chloride system, whereby colorless needle-like crystals were obtained.

IR(KBr)cm<sup>-1</sup>: 2978, 2933, 2235, 1693, 1685, 1572, 1477, 1458, 1415, 1365, 1267, 1238, 1169, 1161, 1124, 1097, 935, 839, 768.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.50(9H,s), 3.05(2H,t,J=5.9Hz),

3.77(2H,t,J=5.9Hz), 4.67(2H,s), 7.54(2H,s).

MS (FAB) m/z: 260 [(M+H)<sup>+</sup>], 204 [(M+H)<sup>+</sup>-isobutene(56)].

Elementary analysis for C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>

Calculated: C, 64.85; H, 6.61; N, 16.20.

Found: C, 64.89; H, 6.60; N, 16.57.

[Referential Example 394] 6-(t-Butoxycarbonyl)-2-methoxycarbonyl-5,6,7,8-tetrahydro-1,6-naphthylidine

To a solution of 6-(t-butoxycarbonyl)-2-cyano-5,6,7,8-tetrahydro-1,6-naphthylidine (1.25 g) in methanol (40 ml), concentrated hydrochloric acid (40 ml) was added at room

temperature and the resulting mixture was stirred at 100°C for 3 hours. After the reaction mixture was allowed to cool down to room temperature, it was gradually poured into tetrahydrofuran (150 ml) and an aqueous solution (250 ml) of sodium carbonate (40 g), which had been stirred in advance, followed by the addition of di-*t*-butyl dicarbonate (1.58 g, 7.23 mmol) at room temperature. The resulting mixture was stirred for 30 minutes. Water (200 ml) was added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue so obtained was purified by chromatography on a silica gel column (100 g of silica gel, methylene chloride : ethyl acetate = 3:1 → 1:1), whereby the title compound (955 mg) was obtained as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.50 (9H, s), 3.12 (2H, t, J=5.9Hz), 3.77 (2H, t, J=5.9Hz), 4.00 (3H, s), 4.67 (2H, s), 7.57 (1H, d, J=8.1Hz), 7.98 (1H, d, J=8.1Hz).

[Referential Example 395] 6-(*t*-Butoxycarbonyl)-2-[[4-(chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthylidine

To a solution of 6-(*t*-butoxycarbonyl)-2-methoxycarbonyl-5,6,7,8-tetrahydro-1,6-naphthylidine (955 mg) in tetrahydrofuran (20 ml), a 3N aqueous solution of

sodium hydroxide (20 ml) was added at room temperature.

After stirring for 2 hours, ammonium sulfate (16.0 g) was added to the reaction mixture. Concentrated hydrochloric acid was added to adjust its pH to 4, followed by

5 extraction with chloroform (2 x 20 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, whereby the residue (874 mg), that is, 6-(t-butoxycarbonyl)-5,6,7,8-tetrahydro-1,6-

naphthylidene-2-carboxylic acid was obtained as a white

10 solid. To a solution of the resulting residue in N,N-dimethylformamide (40 ml), methylene chloride (40 ml) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

hydrochloride (1.42 g) were dissolved, followed by the addition of 1-(dimethylaminopropyl)-3-ethylcarbodiimide

15 (785 mg) and 1-hydroxybenzotriazole (555 mg) at room temperature. Then, diisopropylethylamine (1.71 ml) was added at 0°C. After stirring overnight at room

temperature, a 10% aqueous solution of citric acid (200 ml) and methylene chloride (100 ml) were added to the reaction

20 mixture to cause separation. The organic layer was

extracted with methylene chloride (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was

purified by chromatography on a silica gel column (100 g of  
25 silica gel, methylene chloride : acetone = 10:1 → 5:1).

The white solid thus obtained was reprecipitated in a

methylene chloride - methanol - water system. After filtration and washing with water, the title compound (1.44 g) was obtained as a white solid.

IR(KBr)cm<sup>-1</sup>: 2978, 2924, 2846, 1697, 1637, 1577, 1479,  
5 1454, 1432, 1365, 1340, 1238, 1166, 733, 577.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.50(9H,s), 2.92(2H,t,J=5.7Hz),  
3.11(2H,br t,J=4.4Hz), 3.23(2H,br t,J=4.4Hz),  
3.74(2H,t,J=5.7Hz), 3.78(2H,br t,J=4.4Hz), 3.90(2H,br  
t,J=4.4Hz), 4.59(2H,s), 7.42(1H,br d,J=7.8Hz), 7.47(1H,br  
10 d,J=7.8Hz), 7.58(1H,dd,J=2.0,8.8Hz),  
7.77(1H,dd,J=2.0,8.5Hz), 7.90(1H,d,J=2.0Hz), 7.92-  
7.95(2H,m), 8.30(1H,br s).

MS (FAB) m/z: 571 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 515 [(M+H)<sup>+</sup>-isobutene(56),  
Cl<sup>35</sup>].

15 Elementary analysis for C<sub>28</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>5</sub>S

Calculated: C, 58.89; H, 5.47; N, 9.81; Cl, 6.21; S, 5.61.

Found: C, 58.59; H, 5.61; N, 9.84; Cl, 6.53; S, 5.66.

[Referential Example 396] 2-(t-Butoxycarbonylamino)-3-(t-butyl-  
diphenylsiloxy)propanol

20 At room temperature, imidazole (6.43 g) was added to a  
solution of N-(t-butoxycarbonyl)-L-serine methyl ester  
(13.8 g) in N,N-dimethylformamide (140 ml), followed by the  
addition of t-butyl-diphenylsilyl chloride (19.7 ml) at 0°C.  
The resulting mixture was stirred at room temperature for  
25 39 hours. Ethyl acetate (200 ml) and water (600 ml) were  
added to the reaction mixture to cause separation. The

water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus  
5 obtained was dissolved in tetrahydrofuran (100 ml) and methanol (100 ml) without purification, followed by the addition of sodium borohydride (7.20 g) in portions at 0°C. After stirring at 0°C for 2 hours and then at room temperature for 1 hour, ethyl acetate (100 ml), an aqueous  
10 saturated solution of ammonium chloride (300 ml) and water (300 ml) were added to the reaction mixture to cause separation. The water layer was extracted with ethyl acetate (100 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under  
15 reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (500 g of silica gel, hexane : ethyl acetate = 10:1 → 1:1), whereby the title compound (24.9 g) was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.07(9H,s), 1.44(9H,s), 2.39(1H,br s),  
20 3.63-3.85(5H,m), 5.07(1H,br s), 7.35-7.48(6H,m), 7.60-7.67(4H,m).

[Referential Example 397] 2-(t-Butoxycarbonylamino)-3-(t-butyl-  
diphenylsiloxy)propanal

To a solution of 2-(t-butoxycarbonylamino)-3-(t-butyl-  
25 diphenylsiloxy)propanol (3.03 g) in methylene chloride (100 ml), Dess-Martin periodinane (3.60 g) was added at



room temperature. The resulting mixture was stirred for 30 minutes. To the reaction mixture, a saturated aqueous solution (50 ml) of sodium bicarbonate and a 10% aqueous solution (50 ml) of sodium sulfite were added to cause  
 5 separation. The water layer was extracted with diethyl ether (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (150 g of silica  
 10 gel, hexane : ethyl acetate = 4:1  $\rightarrow$  3:1), whereby the title compound (2.97 g) was obtained as a colorless transparent oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.03(9H,s), 1.46(9H,s),  
 3.93(1H,dd,J=3.9,10.3Hz), 4.18(1H,d,J=2.9,10.3Hz), 4.27-  
 15 4.35(1H,m), 5.33-5.43(1H,m), 7.32-7.48(6H,m), 7.55-  
 7.63(4H,m), 9.66(1H,s).

[Referential Example 398] 1,5-Bis(t-butoxycarbonyl)-2-(t-butyl  
 butyldiphenylsiloxy)methyl-4,5,6,7-tetrahydro-1H-  
 pyrrolo[3,2-c]pyridine

20 To a solution of diisopropylamine (2.35 ml) in tetrahydrofuran (40 ml), n-butyl lithium (a 1.66 N hexane solution, 9.20 ml) was added at 0°C, followed by stirring for 30 minutes. To the reaction mixture, a solution of N-(t-butoxycarbonyl)-4-piperidone (2.77 g) in tetrahydrofuran  
 25 (10 ml) was added at -78°C, and the mixture was stirred for 1.5 hours. To the reaction mixture, a solution of 2-(t-

butoxycarbonylamino)-3-(t-butyldiphenylsiloxy)propanal (2.97 g) in tetrahydrofuran (10 ml) which had been cooled to -78°C was added dropwise. The mixture was warmed up gradually and stirred for 13 hours. Water (150 ml) and diethyl ether (350 ml) were added to the reaction mixture to cause separation. The water layer was extracted with diethyl ether (100 ml). The organic layers were combined, washed with water (100 ml) and saturated aqueous NaCl solution (3 x 100 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was dissolved in methylene chloride (20 ml). Concentrated hydrochloric acid was added dropwise and the mixture was adjusted to pH 5, followed by stirring for 1 hour. Concentrated hydrochloric acid was further added dropwise to adjust its pH to 4, followed by stirring for 1 hour. A saturated aqueous solution (50 ml) of sodium bicarbonate and methylene chloride (20 ml) were added to cause separation. The water layer was extracted with diethyl ether (2 x 50 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (50 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (150 g of silica gel, hexane : ethyl acetate = 8:1 → 4:1), whereby the title compound (2.20 g) was obtained as a colorless transparent caramel-like substance.

IR(KBr)cm<sup>-1</sup>: 2931, 2856, 1738, 1697, 1473, 1427, 1392,  
1367, 1350, 1331, 1232, 1167, 1144, 1109, 1066, 822, 739.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.08(9H,s), 1.43(9H,s), 1.49(9H,s),  
2.89(2H,br s), 3.64(2H,br s), 4.32(2H,s), 4.85(2H,br s),  
5 6.12(1H,s), 7.30-7.48(6H,m), 7.60-7.75(4H,m).

MS(FAB/m-NBA/NaCl) m/z: 613[(M+Na)<sup>+</sup>].

[Referential Example 399] 1,5-Bis(t-butoxycarbonyl)-2-  
hydroxymethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-(t-  
10 butyldiphenylsiloxy)methyl-4,5,6,7-tetrahydro-1H-  
pyrrolo[3,2-c]pyridine (2.10 g) in pyridine (20 ml), a  
mixture of hydrogen fluoride and pyridine was added at 0°C,  
followed by stirring at room temperature for 1 hour. After  
the reaction mixture was poured into ethyl acetate (50 ml)  
15 and ice water (300 ml) which had been stirred in advance,  
the resulting mixture was separated. The water layer was  
extracted with ethyl acetate (50 ml). The organic layers  
were combined, washed with a saturated aqueous solution of  
sodium bicarbonate, dried over anhydrous sodium sulfate and  
20 concentrated under reduced pressure. The residue thus  
obtained was purified by chromatography on a silica gel  
column (150 g of silica gel, hexane : ethyl acetate = 3:1),  
whereby the title compound (882 mg) was obtained as a  
colorless, transparent caramel-like substance.

25 IR(KBr)cm<sup>-1</sup>: 3432, 2976, 2931, 1736, 1695, 1419, 1365,  
1350, 1323, 1234, 1167, 1144, 1105, 754.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47(9H,s), 1.60(9H,s), 2.85(2H,br s),  
3.45-3.70(1H,br), 3.64(2H,br s), 4.29(2H,s),  
4.59(2H,d,  $J=7.3\text{Hz}$ ), 6.01(1H,s).

MS (FAB/m-NBA/NaCl)  $m/z$ : 375  $[(\text{M}+\text{Na})^+]$ .

5 [Referential Example 400] 1,5-Bis(t-butoxycarbonyl)-2-  
formyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-  
hydroxymethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine  
(14.0 mg) in methylene chloride (2.0 ml), Dess-Martin  
10 periodinane (34.0 mg) was added at room temperature. The  
resulting mixture was stirred for 1 hour. To the reaction  
mixture, ethyl acetate (10 ml), a 10% aqueous solution (10  
ml) of sodium thiosulfate and an aqueous solution (10 ml)  
of sodium bicarbonate were added to cause separation. The  
15 water layer was extracted with ethyl acetate (10 ml). The  
organic layers were combined, dried over anhydrous sodium  
sulfate and concentrated under reduced pressure. The  
residue thus obtained was purified by thin-layer  
preparative chromatography on silica gel (hexane : ethyl  
20 acetate = 2:1), whereby the title compound (9.8 mg) was  
obtained as a colorless transparent caramel-like substance.  
IR(KBr) $\text{cm}^{-1}$ : 2976, 2933, 1741, 1697, 1660, 1479, 1413,  
1367, 1346, 1298, 1281, 1234, 1165, 1146, 1103, 895, 850,  
768.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48(9H,s), 1.63(9H,s), 2.96(2H,br

t, J=5.4Hz), 3.68 (2H, br t, J=5.4Hz), 4.37 (2H, s), 6.97 (1H, s), 10.14 (1H, br s).

MS (FAB/m-NBA) m/z: 351 [(M+H)<sup>+</sup>], 295 [(M+H - isobutene(56))<sup>+</sup>], 239 [(M+H) - 2 x isobutene (56))<sup>+</sup>].

5 [Referential Example 401] 1,5-Bis(t-butoxycarbonyl)-2-[[4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine

To a solution of 1,5-bis(t-butoxycarbonyl)-2-formyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (44.0 mg) in  
10 t-butanol (2.0 ml), 2-methyl-2-butene (150  $\mu$ l) and an aqueous solution (6.0 ml) of sodium chlorite (102 mg) and sodium dihydrogenphosphate (135 mg) were added at room temperature. After stirring for 21 hours, the reaction mixture was added with diethyl ether (10 ml) and water (10  
15 ml), followed by the addition of ammonium sulfate until saturation. The resulting mixture was separated, followed by extraction with diethyl ether (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure, whereby the  
20 residue, that is, 1,5-bis(t-butoxycarbonyl)-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid was obtained as a white foamy substance. To a solution of the resulting residue in N,N-dimethylformamide (2.0 ml), methylene chloride (2.0 ml) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (55.0 mg) were  
25 dissolved, followed by the addition of 1-

(dimethylaminopropyl)-3-ethyl carbodiimide (30.5 mg) and 1-hydroxybenzotriazole (21.5 mg) at room temperature. At 0°C, diisopropylethylamine (67.0  $\mu$ l) was added thereto.

After stirring overnight at room temperature, a 10% aqueous citric acid solution (10 ml) and methylene chloride (10 ml) were added to the reaction mixture to cause separation.

The organic layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over

anhydrous sodium sulfate and concentrated under reduced

pressure. The resulting residue was purified by thin-layer preparative chromatography on silica gel (methylene

chloride : acetone = 10:1) and the white solid thus

obtained was reprecipitated in a methylene chloride -

methanol - water system. After filtration and washing

with water, the title compound (50.0 mg) was obtained as a colorless transparent caramel-like substance.

IR(KBr) $\text{cm}^{-1}$ : 2981, 2929, 2860, 1743, 1693, 1647, 1456, 1421, 1367, 1348, 1325, 1279, 1236, 1165, 1103, 955, 945, 729.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.32(9H,s), 1.46(9H,s), 2.83(2H,br t,  $J=5.6\text{Hz}$ ), 3.04(2H,br), 3.17(2H,br), 3.55(2H,br), 3.62(2H,br t,  $J=5.6\text{Hz}$ ), 3.82(2H,br), 4.25(2H,s), 5.94(1H,s), 7.59(1H,dd,  $J=2.0, 8.8\text{Hz}$ ), 7.76(1H,dd,  $J=1.7, 8.5\text{Hz}$ ), 7.87-7.98(3H,m), 8.30(1H,br s).

MS (FAB/m-NBA/NaCl) m/z: 681 [(M+Na)<sup>+</sup>], 581 [(M+Na-Boc(100))<sup>+</sup>], 525 [(M+Na-Boc(100)-isobutene(56))<sup>+</sup>].

[Referential Example 402] 1-(tert-Butoxycarbonyl)-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

To a solution of lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (293 mg) in N,N-dimethylformamide (10 ml) were added 1-(tert-butoxycarbonyl)piperazine (294 mg), 1-hydroxybenzotriazole monohydrate (214 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (303 mg) at room temperature. After stirring for 38 hours, methylene chloride (20 ml) and water (200 ml) were added to the reaction mixture to separate it into layers. The water layer thus obtained was extracted with methylene chloride (3 x 10 ml). The organic layers were combined, washed with a saturated aqueous solution (100 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 2:1), whereby the title compound (300 mg) was obtained as a pale yellow viscous substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48(9H,s), 2.51(3H,s), 2.83(2H,t,J=5.7Hz), 2.94(2H,t,J=5.7Hz), 3.53(4H,t,J=5.2Hz), 3.71(2H,s), 3.75(2H,br s), 4.38(2H,br s).

MS (FAB)  $m/z$ : 367 ( $M+H$ )<sup>+</sup>, 311 ( $M$ -isobutene +  $H$ )<sup>+</sup>, 267 ( $M$ -Boc +  $H$ )<sup>+</sup>.

[Referential Example 403] Thiazolo[4,5-*c*]pyridine

In formic acid (60 ml) was dissolved 3-(tert-butoxyamino)-4-mercaptopyridine (9.20 g), followed by heating under reflux for 4 hours. After the reaction mixture was concentrated under reduced pressure and a 5N aqueous solution (100 ml) of potassium hydroxide was added to the residue, the resulting mixture was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. Diethyl ether was added to the residue and the solid so precipitated was collected by filtration, whereby the title compound was obtained as a colorless solid (3.97 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 7.93(1H, d,  $J=5.4$ Hz), 8.60(1H, d,  $J=5.4$ Hz), 9.07(1H, s), 9.46(1H, s).

[Referential Example 404] 5-Methyl-4,5,6,7-tetrahydrothiazolo[4,5-*c*]pyridine

In N,N-dimethylformamide (80 ml) was dissolved thiazolo[4,5-*c*]pyridine (700 mg), followed by the addition of methyl iodide (0.65 ml). The resulting mixture was stirred under heat at 80°C for 4 hours. After concentration of the reaction mixture under reduced pressure, the residue was dissolved in water (100 ml). Sodium borohydride (583 mg) was added to the resulting



solution, followed by stirring at room temperature for 1 hour. After the addition of a saturated aqueous solution of potassium carbonate, the resulting mixture was extracted with ether. The organic layer thus extracted was dried  
5 over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 25:1), whereby the title compound (596 mg) was obtained as a colorless oil.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.52(3H,s), 2.77(2H,t,J=5.4Hz), 2.92-3.00(2H,m), 3.69(2H,t,J=2.0Hz), 8.61(1H,s).

MS (FAB)  $m/z$ : 155 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 405] Lithium 5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-carboxylate

15 In anhydrous tetrahydrofuran (10 ml) was dissolved 5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine (583 mg), followed by the dropwise addition of a hexane solution (1.54M, 2.70 ml) of n-butyl lithium at  $-78^\circ\text{C}$ . After stirring for 10 minutes, the reaction mixture was warmed up  
20 to  $0^\circ\text{C}$  and stirring was conducted for 30 minutes. The reaction mixture was cooled to  $-78^\circ\text{C}$ . A carbon dioxide gas was blown into the reaction mixture for 15 minutes, followed by warming up to room temperature. The reaction mixture was concentrated under reduced pressure, whereby  
25 the title compound (820 mg) was obtained as a pale brown foamy solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.38 (3H, s), 2.64 (2H, br s), 2.80 (2H, br s), 3.44 (2H, br s).

MS (FD) m/z: 199 (M+H)<sup>+</sup>.

[Referential Example 406] Lithium thiazolo[4,5-c]pyridine-  
5 2-carboxylate

In the same manner as in Referential Example 405, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 8.07 (1H, d, J=5.4Hz), 8.48 (1H, d, J=5.4Hz), 9.22 (1H, s).

10 [Referential Example 407] 5-Isopropyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine

In the same manner as in Referential Example 404, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.16 (6H, d, J=6.8Hz), 2.80-2.92 (4H, m),  
15 2.95-3.03 (1H, m), 3.83 (2H, t, J=2.0Hz), 8.60 (1H, s).

MS (FAB) m/z: 183 (M+H)<sup>+</sup>.

[Referential Example 408] Lithium 5-isopropyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-carboxylate

20 In the same manner as in Referential Example 405, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.64 (2H, br s), 2.80 (2H, br s), 3.44 (2H, br s).

MS (FAB) m/z: 277 (M+H)<sup>+</sup>.

[Referential Example 409] 1-Benzoyl-3-bromo-2-methyl-4-  
25 piperidone

In diethyl ether (50 ml) was suspended copper cyanide (197 mg), followed by the dropwise addition of a diethyl ether solution (1.10 mole, 4.00 ml) of methyl lithium at -78°C. The reaction mixture was warmed up to 0°C. After  
5 the reaction mixture was stirred for 10 minutes, it was cooled to -78°C again. To the reaction mixture was added dropwise a diethyl ether solution (5 ml) of N-benzoylazacyclohexa-2-en-4-one (400 mg) (Can. J. Chem., 1981, 3136-3140) at -78°C, followed by stirring for 30  
10 minutes. After trimethylsilyl chloride (0.53 ml, 4.20 mmol) was added dropwise to the reaction mixture, the resulting mixture was warmed up to room temperature. The reaction mixture was added with a saturated aqueous solution of sodium bicarbonate. The resulting solution was  
15 then extracted with ethyl acetate. The organic layer thus extracted was washed with aqueous NaCl solution. The extract was dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was dissolved in acetone (10 ml), followed by the addition of sodium  
20 acetate (135 mg), water (2 ml) and N-bromosuccinic imide (292 mg) under ice cooling. The resulting mixture was stirred overnight at room temperature. To the reaction mixture was added an aqueous solution of sodium thiosulfate (2 moles, 10 ml). After stirring for 30 minutes, ethyl  
25 acetate was added and the organic layer was collected. The organic layer thus obtained was washed with saturated

aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:3), whereby the title compound (240 mg) was obtained as a yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.39(3H,d,J=7.3Hz), 2.20-2.40(1H,m), 2.65(1H,br s), 3.18-3.58(2H,m), 4.01(1H,br s), 4.15-4.62(1/2H,m), 4.80-5.28(1/2H,m), 7.40-7.55(5H,m).

MS (FAB)  $m/z$ : 296 ( $\text{M}^+$ ,  $\text{Br}^{79}$ ), 298 ( $\text{M}^+$ ,  $\text{Br}^{81}$ ).

[Referential Example 410] 6-Benzoyl-7-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

In butanol (20 ml) was dissolved 1-benzoyl-2-methyl-3-bromo-4-piperidone (240 mg), followed by the addition of thioformamide (160 mg). The resulting mixture was stirred at 100°C for 2.5 hours. After the reaction mixture was cooled to room temperature, it was subjected to Celite filtration. The filtrate was washed with a saturated aqueous solution of sodium bicarbonate and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:2), whereby the title compound (56 mg) was obtained as a yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.39(3H,d,J=5.6Hz), 2.88-3.10(2H,m), 3.41(1H,br s), 3.94(1H,br s), 5.97(1H,br s), 7.38-7.48(5H,m), 8.70(1H,s).

MS (FAB)  $m/z$ : 259 (M+H)<sup>+</sup>.

[Referential Example 411] 6-tert-Butoxycarbonyl-7-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

Under ice cooling, sodium hydride (60% in oil, 270 mg) was added to butanol (70 ml), followed by stirring for 30 minutes. A butanol solution (5 ml) of 6-benzoyl-7-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (240 mg) was added to the reaction mixture. The resulting mixture was heated under reflux for 4 days. After water (5 ml) was added to the reaction mixture and the mixture was heated under reflux for 30 minutes, the reaction mixture was cooled to room temperature. To the reaction mixture was added di-tert-butyl dicarbonate (883 mg) and they were stirred at room temperature for 8 hours. The reaction mixture was concentrated under reduced pressure. To the residue were added 3N hydrochloric acid (10 ml) and ethyl acetate to separate the resulting mixture into layers. The organic layer thus collected was dried over anhydrous sodium sulfate and distilled to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:4), whereby the title compound (168 mg) was obtained as a yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.46(3H,d,J=5.6Hz), 1.49(9H,s), 2.85-2.92(2H,m), 3.10(1H,m), 4.27-4.50(1H,m), 5.23-5.52(1H,m), 8.65(1H,s).

MS (FAB)  $m/z$ : 255 (M+H)<sup>+</sup>.

[Referential Example 412] Lithium 6-(tert-butoxycarbonyl)-7-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate

5 In the same manner as in Referential Example 405, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.38-1.40(3H,m), 1.43(9H,s), 2.60-2.82(2H,m), 3.11(1H,br s), 4.15(1H,br s), 5.10-5.32(1H,m).  
MS (FAB)  $m/z$ : 298  $\text{M}^+$ .

[Referential Example 413] 4-Ethoxycarbonylthiazole

10 Formamide (100 ml) was stirred under ice cooling, followed by the addition of diphosphorus pentasulfide (27.48 g) in the form of a solid. The resulting mixture was stirred overnight at room temperature. Water (200 ml) was added and then the mixture was extracted with diethyl  
15 ether (8 x 200 ml). The organic layers were combined, washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby thioformamide (35.8 g) was obtained as a yellow oil. While stirring, ethyl  
20 bromopyruvate (20.0 g) was added to the resulting oil. After the addition of ethanol (100 ml) to the reaction mixture, ethyl bromopyruvate (45.04 g) was added further. The resulting mixture was stirred at room temperature for 3 hours. The solvent was distilled off under reduced  
25 pressure. Methylene chloride was added to the residue. The resulting mixture was washed with a saturated aqueous

solution of sodium bicarbonate and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (42.73 g) was obtained as a brown oil.

5  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.43(3H,t,J=7.3Hz), 4.45(2H,q,J=7.3Hz), 8.26(1H,d,J=2.0Hz), 8.86(1H,d,J=2.0Hz).

MS (EI)  $m/z$ : 157  $\text{M}^+$ .

[Referential Example 414] 4-Formylthiazole

10 In anhydrous tetrahydrofuran (150 ml) was dissolved 4-ethoxycarbonylthiazole (15.2 g) and the resulting solution was cooled to  $-78^\circ\text{C}$ . Diisobutylaluminum hydride (a 0.95 mole hexane solution, 102 ml) was added dropwise, followed by stirring for 1 hour at a temperature maintained at  $-78^\circ\text{C}$ . After the addition of methanol (20 ml) and heating  
15 to room temperature, the reaction mixture was subjected to Celite filtration. The precipitate so obtained was washed with tetrahydrofuran and ethyl acetate and then added to a saturated aqueous solution of ammonium chloride. The resulting mixture was extracted with methylene chloride.  
20 The organic layers were combined and distilled under reduced pressure to remove the solvent. The residue was then dissolved in methylene chloride. The resulting solution was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under  
25 reduced pressure to remove the solvent, whereby the title compound (7.37 g) was obtained as a yellow solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 8.27 (1H, d,  $J=2.0\text{Hz}$ ), 8.92 (1H, d,  $J=2.0\text{Hz}$ ), 10.15 (1H, s).

MS (EI)  $m/z$ : 113  $\text{M}^+$ .

[Referential Example 415] 4-(2-Nitro-1-propenyl)thiazole

5        In isopropyl alcohol (100 ml) was dissolved 4-formylthiazole (10.9 g), followed by the addition of potassium fluoride (280 mg) and nitromethane (14.46 g). The resulting mixture was stirred at 60 to 65°C for 2 hours. The reaction mixture was then stirred overnight at  
10       room temperature. The solvent was distilled off under reduced pressure. The residue was dissolved in benzene (50 ml), followed by the addition of acetic anhydride (12.29 g) and 4-(dimethylamino)pyridine (588 g). The resulting mixture was heated under reflux for 2 hours. The solvent  
15       was distilled off under reduced pressure. Methylene chloride was added to the residue. The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was then dried over anhydrous sodium sulfate and distilled under reduced  
20       pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 1:1), whereby the title compound (8.73 g) was obtained as vividly yellow crystals.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.78 (3H, d,  $J=0.5\text{Hz}$ ), 7.68 (1H, d,  $J=2.0\text{Hz}$ ),  
25       8.03 (1H, m), 8.92 (1H, d,  $J=2.0\text{Hz}$ ).



MS (EI) m/z: 170 M<sup>+</sup>.

[Referential Example 416] 4-[2-[N-(tert-Butoxycarbonyl)amino]propyl]thiazole

Under ice cooling, lithium aluminum hydride (2.41 g)  
5 was suspended in anhydrous tetrahydrofuran (50 ml). An  
anhydrous tetrahydrofuran solution (90 ml) of 4-(2-nitro-1-  
propenyl)thiazole (10.8 g) was added dropwise to the  
resulting suspension. After stirring at the same  
temperature for 40 minutes, sodium sulfate 10 hydrate (15  
10 g) was added and the resulting mixture was stirred for 45  
minutes. The reaction mixture was subjected to Celite  
filtration. From the precipitate, an organic substance was  
extracted with hot methanol. The organic layers were  
combined and distilled under reduced pressure to remove the  
15 solvent. Methylene chloride (50 ml), sodium carbonate (3.4  
g) and di-tert-butyl dicarbonate (13.86 g) were added to  
the residue, followed by stirring at room temperature for 2  
hours. The reaction mixture was washed with water, dried  
over anhydrous sodium sulfate and distilled under reduced  
20 pressure to remove the solvent. The residue was purified  
by chromatography on a silica gel column ( $\Phi$  4 x 20 cm,  
hexane : ethyl acetate = 3:1  $\rightarrow$  3:2), whereby the title  
compound (2.86 g) was obtained as a brown oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.13, 1.16 (total 3H, d each,  $J=6.6, 6.4\text{Hz}$ ), 1.42 (9H, s), 2.91-3.09 (2H, m), 4.00-4.11 (1H, m), 5.03-5.08 (1H, m), 7.05-7.10 (1H, m), 8.75-8.77 (1H, m).

MS (FAB)  $m/z$ : 243 ( $\text{M}+\text{H}$ ) $^+$ .

5 [Referential Example 417] 6-(tert-Butoxycarbonyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

In ethanol (26 ml) was dissolved 4-[2-[N-(tert-butoxycarbonyl)amino]propyl]thiazole (1.07 g), followed by the addition of paraformaldehyde (90%, 2.94 g) and a 1N solution (13 ml) of hydrochloride in ethanol. The resulting mixture was charged in a sealed tube and stirred at 100°C for 28 hours. During stirring, operation of cooling to room temperature, loosening the lid and thereby reducing the internal pressure of the tube was carried out several times. The solvent was then distilled off under reduced pressure. To the residue were added methylene chloride (18 ml), triethylamine (2.6 ml) and di-tert-butyl dicarbonate (1.45 g), followed by stirring at room temperature for 3 hours. The reaction mixture was washed with water, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography (hexane : ethyl acetate = 4:1) using, as a carrier, silica gel, whereby the title compound (625 mg) was obtained as a pale yellow solid.

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$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.15 (3H, d,  $J=6.8\text{Hz}$ ), 1.49 (9H, s),  
2.77 (1H, d,  $J=16.6\text{Hz}$ ), 3.09-3.14 (1H, m), 4.21 (1H, d,  $J=16.8\text{Hz}$ ),  
4.84 (1H, br s), 5.06 (1H, br s), 8.69 (1H, s).  
MS (FAB)  $m/z$ : 255 ( $M+H$ ) $^+$ .

5 [Referential Example 418] 4-Formyl-2-(trans- $\beta$ -styryl)oxazole

To a solution of 4-ethoxycarbonyl-2-(trans- $\beta$ -styryl)oxazole (8.57 g) (J. Org. Chem. 1996, 61, 6496-6497) in methylene chloride (80 ml) was added dropwise  
10 diisobutylaluminum hydride (a 1.0 mole hexane solution, 66.0 ml) at  $-78^\circ\text{C}$ . After stirring for 15 minutes, methanol (11 ml) was added dropwise and the resulting mixture was warmed up to room temperature over 1 hour. The reaction mixture was then subjected to Celite filtration. The pasty  
15 substance thus obtained was dissolved in ethyl acetate (200 ml) and a saturated aqueous solution (200 ml) of ammonium chloride. The resulting solution was separated into layers. The water layer was extracted with methylene chloride (2 x 100 ml). The organic layers were combined  
20 and washed with a saturated aqueous solution (100 ml) of sodium bicarbonate and saturated aqueous NaCl solution (100 ml), followed by the addition of the filtrate upon Celite filtration. The resulting mixture was dried over anhydrous sodium sulfate and distilled under reduced pressure to  
25 remove the solvent. The residue was purified by

chromatography on a silica gel column (methylene chloride : ethyl acetate = 5:1 → methylene chloride : methanol = 10:1), whereby the title compound (5.86 g) was obtained as colorless needle crystals.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 6.96(1H,d,J=16.6Hz), 7.35-7.45(3H,m), 7.56(2H,d,J=6.4Hz), 7.67(1H,d,J=16.6Hz), 8.26(1H,s), 9.98(1H,s).

MS (FAB)  $m/z$ : 200 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 419] 2-(trans- $\beta$ -Styryl)-4-

10 vinyloxazole

To a solution of (methyl)triphenylphosphonium bromide (8.16 g, 22.8 mmol) in tetrahydrofuran (80 ml) was added dropwise *n*-butyl lithium (a 1.54N hexane solution, 14.2 ml) at 0°C, followed by stirring at room temperature for 30  
15 minutes. The reaction mixture was cooled to 0°C again and a solution of 4-formyl-2-(trans- $\beta$ -styryl)oxazole (3.64 g) in tetrahydrofuran (20 ml) was added thereto. The resulting mixture was heated to room temperature. After stirring for 2 hours, water (200 ml) and ethyl acetate (100  
20 ml) were added to separate the reaction mixture into layers. The water layer was extracted with ethyl acetate (50 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (100 ml), dried over anhydrous sodium sulfate and distilled under reduced  
25 pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column (hexane : ethyl acetate = 4:1 → 3:1), whereby the title compound (2.84 g) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 5.33 (1H, dd,  $J=10.7, 1.5\text{Hz}$ ),

5 5.98 (1H, dd,  $J=17.6, 1.5\text{Hz}$ ), 6.56 (1H, dd,  $J=17.6, 10.7\text{Hz}$ ),  
6.95 (1H, d,  $J=16.6\text{Hz}$ ), 7.31-7.42 (3H, m), 7.49-7.56 (4H, m).

MS (FAB)  $m/z$ : 198 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 420] 4-(2-Hydroxyethyl)-2-(trans- $\beta$ -styryl)oxazole

10 To a solution of 2-(trans- $\beta$ -styryl)-4-vinyloxazole  
(13.0 g) in tetrahydrofuran (500 ml) was added 9-  
borabicyclo[3.3.1]nonane (a 0.5 mole tetrahydrofuran  
solution, 158 ml) at 0°C. The resulting mixture was  
stirred at room temperature for 15 hours. At 0°C, water  
15 (10 ml), a 3N aqueous solution of sodium hydroxide (80 ml)  
and aqueous hydrogen peroxide (80 ml) were successively  
added dropwise to the reaction mixture, followed by  
stirring at room temperature for 6 hours. Water (600 ml)  
and ethyl acetate (200 ml) were added to the reaction  
20 mixture to separate the reaction mixture into layers. The  
water layer was extracted with ethyl acetate (200 ml). The  
organic layers were combined, washed with saturated aqueous  
NaCl solution (200 ml), dried over anhydrous sodium sulfate  
and distilled under reduced pressure to remove the solvent.  
25 The residue was purified by chromatography on a silica gel

column (hexane : ethyl acetate = 2:1 → only ethyl acetate), whereby the title compound (14.1 g) was obtained as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.69 (1H, br s), 2.80 (2H, t, J=5.6 Hz), 3.90-3.97 (2H, m), 6.91 (1H, d, J=16.6 Hz), 7.30-7.42 (4H, m), 7.43-7.56 (3H, m).

MS (FAB) m/z: 216 (M+H)<sup>+</sup>.

[Referential Example 421] N-[2-[2-(trans-β-styryl)oxazol-4-yl]ethyl]phthalimide

To a solution of 4-(2-hydroxyethyl)-2-(trans-β-styryl)oxazole (292 mg) in tetrahydrofuran (15 ml) were added phthalimide (200 mg), triphenylphosphine (357 mg) and diethyl azodicarboxylate (214 μl) at room temperature, followed by stirring for 4 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby the title compound (447 mg) was obtained as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.98 (2H, t, J=7.2 Hz), 4.03 (2H, t, J=7.2 Hz), 6.88 (1H, d, J=16.6 Hz), 7.28-7.45 (5H, m), 7.48 (2H, d, J=7.3 Hz), 7.71 (2H, dd, J=5.4, 2.9 Hz), 7.84 (2H, dd, J=5.4, 2.9 Hz).

MS (FAB) m/z: 345 (M+H)<sup>+</sup>.

[Referential Example 422] 4-[2-(tert-Butoxycarbonylamino)ethyl]-2-(trans-β-styryl)oxazole

To a solution of N-[2-[2-(trans- $\beta$ -styryl)oxazol-4-yl]ethyl]phthalimide (6.40 g) in ethanol (150 ml) was added hydrazine monohydrate (1.50 ml) at room temperature. After stirring for 1 hour, hydrazine monohydrate (500  $\mu$ l) was added again at room temperature, followed by stirring for 2 hours. At room temperature, methylene chloride (150 ml) and a saturated aqueous solution (150 ml) of sodium bicarbonate and di-tert-butyl dicarbonate (13.4 g, 61.4 mmol) were added to the reaction mixture. After stirring for 30 minutes, the reaction mixture was separated into layers. The water layer was extracted with methylene chloride (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1  $\rightarrow$  1:1), whereby the title compound (5.06 g) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45(9H,s), 2.75(2H,t,J=6.6Hz), 3.46(2H,dt,J=5.9,6.6Hz), 4.92(1H,br s), 6.91(1H,d,J=16.6Hz), 7.29-7.45(4H,m), 7.48(1H,d,J=16.6Hz), 7.52(2H,d,J=7.3Hz).

MS (FAB)  $m/z$ : 315 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 423] 6-(tert-Butoxycarbonyl)-2-(trans- $\beta$ -styryl)-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine

To a solution of 4-[2-(tert-Butoxycarbonylamino)ethyl]-2-(trans- $\beta$ -styryl)oxazole (190 mg) in toluene (15 ml) were added paraformaldehyde (54.5 mg) and p-toluenesulfonic acid (7.2 mg) at room temperature. After heating under reflux for 1 hour, the reaction mixture was allowed to cool down. Ethyl acetate (15 ml) and a saturated aqueous solution (15 ml) of sodium bicarbonate were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1  $\rightarrow$  2:1), whereby the title compound (153 mg) was obtained as a colorless transparent viscous substance.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 (9H, s), 2.67 (2H, br s), 3.73 (2H, br s), 4.55 (2H, s), 6.90 (1H, d,  $J=16.1\text{Hz}$ ), 7.29-7.42 (3H, m), 7.46 (1H, d,  $J=16.1\text{Hz}$ ), 7.52 (2H, d,  $J=7.3\text{Hz}$ ). MS (FAB)  $m/z$ : 327 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 424] 6-(tert-Butoxycarbonyl)-2-formyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine

To a solution of 6-(tert-butoxycarbonyl)-2-(trans- $\beta$ -styryl)-4,5,6,7-tetrahydrooxazol[5,4-c]pyridine (803 mg) in tetrahydrofuran (16 ml) were added acetone (8.0 ml), water (4.0 ml), N-methylmorpholine oxide (577 mg) and osmium



tetraoxide (a 0.039 mole aqueous solution, 3.20 ml) at room temperature, followed by stirring overnight. Ethyl acetate (50 ml) and a 10% aqueous solution (50 ml) of sodium thiosulfate were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (30 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. A solution of the resulting residue in tetrahydrofuran (16 ml) were added methanol (8.0 ml), water (8.0 ml) and sodium metaperiodate (790 mg) at room temperature. After stirring for 3 hours, ethyl acetate (30 ml) and water (50 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (20 ml). The organic layers were combined, washed with a saturated aqueous solution of sodium bicarbonate (50 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1 → 2:1), whereby the title compound (234 mg) was obtained as a colorless transparent glassy substance.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49(9H,s), 2.77(2H,br s), 3.77(2H,br s), 4.62(2H,s), 9.70(1H,s).

The resulting aldehyde was unstable so that it was provided for the subsequent reaction immediately.

[Referential Example 425] 6-(tert-Butoxycarbonyl)-2-methoxycarbonyl-4,5,6,7-tetrahydrooxazol[5,4-c]pyridine

To a solution of 6-(tert-butoxycarbonyl)-2-formyl-4,5,6,7-tetrahydrooxazol[5,4-c]pyridine (225 mg) in methanol (9.0 ml) were added sodium cyanide (220 mg) and manganese dioxide (780 mg) at room temperature, followed by stirring for 30 minutes. The reaction mixture was subjected to Celite filtration by using ethyl acetate. The filtrate was washed with water (50 ml) and saturated saline (50 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:2 → 1:1), whereby the title compound (120 mg) was obtained as a colorless transparent glassy substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.49(9H,s), 2.73(2H,br s), 3.74(2H,br s), 4.01(3H,s), 4.59(2H,s).

MS (FAB) m/z: 283 (M+H)<sup>+</sup>.

[Referential Example 426] Lithium 6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrooxazol[5,4-c]pyridine-2-carboxylate

To a solution of 6-(tert-butoxycarbonyl)-2-methoxycarbonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine (311 mg) in tetrahydrofuran (8.0 ml) were added water (2.0 ml) and lithium hydroxide (25.0 mg) at room temperature. After stirring for 10 minutes, the reaction mixture was distilled under reduced pressure to remove the solvent,

whereby the title compound (280 mg) was obtained as a colorless solid. The residue was provided for the subsequent reaction without purification.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.42(9H,s), 3.31(2H,s),  
5 3.60(2H,d,J=5.4Hz), 4.42(2H,s).

[Referential Example 427] 2-Methoxycarbonyl-6-methyl-  
4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine

To a solution of 6-(tert-butoxycarbonyl)-2-  
methoxycarbonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine  
10 (500 mg) in methylene chloride (15 ml) was added  
trifluoroacetic acid (15 ml) at room temperature, followed  
by stirring for 10 minutes. The reaction mixture was  
concentrated under reduced pressure. To the resulting  
residue were added methylene chloride (20 ml),  
15 triethylamine (495  $\mu\text{l}$ ), acetic acid (205  $\mu\text{l}$ ), formalin (230  
 $\mu\text{l}$ ) and sodium triacetoxyborohydride (570 mg) at room  
temperature. After stirring for 15 minutes, methylene  
chloride (20 ml) and a saturated aqueous solution (50 ml)  
of sodium bicarbonate were added to the reaction mixture to  
20 separate it into layers. The water layer was extracted  
with methylene chloride (3 x 20 ml). The organic layers  
were combined, dried over anhydrous sodium sulfate and  
distilled under reduced pressure to remove the solvent.  
The residue was purified by chromatography on a silica gel  
25 column (chloroform : methanol = 20:1  $\rightarrow$  10:1), whereby the

title compound (257 mg) was obtained as a colorless transparent oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.52(3H,s), 2.72-2.78(2H,m), 2.78-2.83(2H,m), 3.61(2H,t,  $J=1.7\text{Hz}$ ), 4.00(3H,s).

5 MS (FAB)  $m/z$ : 197 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 428] 1-(tert-Butoxycarbonyl)-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

To a solution of 2-methoxycarbonyl-6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine (250 mg) in  
10 tetrahydrofuran (8.0 ml) were added water (2.0 ml) and lithium hydroxide (30.0 mg) at room temperature. After stirring for 10 minutes, the solvent was distilled off under reduced pressure. To a solution of the resulting  
15 residue in  $N,N$ -dimethylformamide (4.0 ml) were added 1-(tert-butoxycarbonyl)piperazine (260 mg), 1-hydroxybenzotriazole monohydrate (189 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (268 mg) at room temperature. After stirring for 63 hours,  
20 methylene chloride (20 ml) and a saturated aqueous solution (30 ml) of sodium bicarbonate were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined and washed with water (150 ml). The  
25 resulting water layer was extracted with methylene chloride (3 x 10 ml). The organic layers were combined, dried over

anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 1:1 → 1:3), whereby the title compound (359 mg) was obtained as a colorless transparent viscous substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48(9H,s), 2.51(3H,s), 2.71(2H,t,J=4.5Hz), 2.79(2H,t,J=4.5Hz), 3.51(4H,t,J=5.0Hz), 3.60(2H,s), 3.75(2H,t,J=5.0Hz), 4.22(2H,t,J=5.0Hz).

MS (FAB) m/z: 351 (M+H)<sup>+</sup>.

[Referential Example 429] 6-(tert-Butoxycarbonyl)-2-methylthio-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

To a solution of 1-(tert-butoxycarbonyl)-4-piperidone (9.30 g) in tetrahydrofuran (40 ml) was added N,N-dimethylformamide dimethylacetal (18.6 ml) at room

temperature, followed by heating under reflux for 3 days.

After the reaction mixture was allowed to cool down to room temperature, it was concentrated under reduced pressure.

To a solution of the resulting residue in ethanol (120 ml) were added methylisothiourea sulfate (19.5 g) and sodium

ethoxide (13.2 g) at room temperature, followed by heating under reflux for 5 hours. After the reaction mixture was

allowed to cool down, water (700 ml) and ethyl acetate (200 ml) were added to the reaction mixture to separate it into

layers. The water layer was then extracted with ethyl

acetate (200 ml). The organic layers were combined, washed with saturated saline (200 ml), dried over anhydrous sodium

sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 20:1 → 15:1), whereby the title compound (1.82 g) was obtained as a colorless transparent viscous substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.49(9H,s), 2.56(3H,s), 2.89(2H,t,J=5.9Hz), 3.72(2H,t,J=5.9Hz), 4.52(2H,s), 8.27(1H,s).

MS (FAB) m/z: 282 (M+H)<sup>+</sup>.

[Referential Example 430] 6-(tert-Butoxycarbonyl)-2-methylsulfonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

To a solution of 6-(tert-butoxycarbonyl)-2-methylthio-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (2.20 g) in methylene chloride (80 ml) was added metachloroperbenzoic acid (3.37 g). After stirring for 4 hours, a 10% aqueous solution (100 ml) of sodium thiosulfate and a saturated aqueous solution (100 ml) of sodium bicarbonate were added to the reaction mixture and the mixture was separated into layers. The water layer was extracted with methylene chloride (2 x 50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 20:1 → 10:1), whereby the title compound (2.34 g) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 (9H, s), 3.10 (2H, t,  $J=5.9\text{Hz}$ ),  
3.34 (3H, s), 3.80 (2H, t,  $J=5.9\text{Hz}$ ), 4.71 (2H, s), 8.63 (1H, s).

MS (FAB)  $m/z$ : 314 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 431] 6-(tert-Butoxycarbonyl)-2-cyano-  
5,6,7,8-tetrahydrocyano[4,3-d]pyrimidine

To a solution of 6-(tert-butoxycarbonyl)-2-methylsulfonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (330 mg) in methylene chloride (10 ml) was added tetrabutylammonium cyanide (425 mg) at room temperature. After stirring at room temperature for 3 hours, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 20:1), whereby the title compound (261 mg) was obtained as pale yellow foam.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 (9H, s), 3.02 (2H, t,  $J=5.9\text{Hz}$ ),  
3.78 (2H, t,  $J=5.9\text{Hz}$ ), 4.68 (2H, s), 8.55 (1H, s).

MS (FAB)  $m/z$ : 261 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 432] 6-(tert-Butoxycarbonyl)-2-methoxycarbonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

To a solution of 6-(tert-butoxycarbonyl)-2-cyano-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (814 mg) in methanol (10 ml) was added concentrated sulfuric acid (5.0 ml) at room temperature. The resulting mixture was stirred at 100°C for 1 hour. After the reaction mixture was allowed to cool down, it was concentrated under reduced

pressure. The residue was dissolved in methylene chloride (15 ml), followed by the addition of triethylamine (2.20 ml) and di-tert-butyl dicarbonate (1.03 g) at room temperature. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 6:1 → 3:1), whereby the title compound (619 mg) was obtained as a pale yellow viscous substance.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50 (9H, s), 3.10 (2H, t,  $J=5.8\text{Hz}$ ), 3.79 (2H, t,  $J=5.8\text{Hz}$ ), 4.06 (3H, s), 4.71 (2H, s), 8.65 (1H, s).

MS (FAB)  $m/z$ : 294 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 433] Lithium 6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine-2-carboxylate

In the same manner as in Referential Example 371, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ : 2.30-2.60 (4H, m), 2.35 (3H, s), 3.34 (2H, s), 6.50 (1H, s).

[Referential Example 434] 1-(tert-Butoxycarbonyl)-4-[(6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.



$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48(9H,s), 2.49(3H,s), 2.55-2.65(2H,m),  
2.65-2.75(2H,m), 3.45-3.55(6H,m), 3.76(4H,br s),  
6.86(1H,s).

MS (FAB)  $m/z$ : 350 ( $\text{M}+\text{H}$ ) $^+$ .

5 [Referential Example 435] Methyl 2-tert-  
butoxycarbonylisoindoline-5-carboxylate

In the same manner as in Referential Example 363, the  
title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.52(9H,s), 3.92(3H,s), 4.65-4.72(2H,m),  
10 4.73(2H,s), 7.29(0.5H,d,J=7.8Hz), 7.34(0.5H,d,J=7.8Hz),  
7.91(0.5H,s), 7.96(1H,s), 7.98(0.5H,s).

MS (FAB)  $m/z$ : 278 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{15}\text{H}_{19}\text{NO}_4$

Calculated: C, 64.97; H, 6.91; N, 5.05.

15 Found: C, 64.94; H, 7.13; N, 4.96.

In the same manner as in Referential Example 368,  
compounds shown in Referential Examples 436 and 437 were  
obtained.

[Referential Example 436] 2-tert-  
20 Butoxycarbonylisoindoline-5-carboxylic acid

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.53(9H,s), 4.70-4.72(2H,m), 4.75(2H,s),  
7.32(0.5H,d,J=7.3Hz), 7.38(0.5H,d,J=7.3Hz), 7.97(0.5H,s),  
8.02(1H,s), 8.04(0.5H,s).

MS (FAB)  $m/z$ : 264 ( $\text{M}+\text{H}$ ) $^+$ .

25 Elementary analysis for  $\text{C}_{14}\text{H}_{17}\text{NO}_4$

Calculated: C, 63.87; H, 6.51; N, 5.32.

Found: C, 63.79; H, 6.65; N, 5.12.

[Referential Example 437] 4-tert-Butoxycarbonyl-3-carboxymethyl-1-[(5-chloroindol-2-yl)sulfonyl]piperazine

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.33(9H,s), 2.12-2.25(1H,m), 2.30-2.42(2H,m), 2.35-3.57(1H,m), 2.60-2.71(1H,m), 2.90-3.02(1H,m), 3.54-3.65(1H,m), 3.72-3.86(2H,m), 4.43(1H,br s), 6.99(1H,s), 7.30(1H,dd,J=8.8,1.8Hz), 7.48(1H,d,J=8.8Hz), 7.75(1H,d,J=1.8Hz).

10 MS (FAB)  $m/z$ : 480 ( $\text{M}+\text{Na}$ ) $^+$ .

[Referential Example 438] 4-tert-Butoxycarbonyl-1-[(5-chloroindol-2-yl)sulfonyl]-3-[N-(2-hydroxyethyl)carbamoylmethyl]piperazine

In the same manner as in Referential Example 5, the  
15 title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40(9H,s), 2.30-2.90(3H,m), 3.03-4.15(7H,m), 4.62-4.71(1H,m), 6.56(1H,br s), 6.95(1H,s), 7.28(1H,dd,J=8.8,1.7Hz), 7.37(1H,d,J=8.8Hz), 7.64(1H,d,J=1.7Hz), 10.01-10.70(1H,br m).

20 FAB-MS  $m/z$ : 502 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 504 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 439] 4-[(5-Chloro-1-phenylsulfonyl-indol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-(2-hydroxyethyl)piperazine

In tetrahydrofuran - methanol (10/1, 55 mL) was  
25 dissolved 4-(tert-butoxycarbonyl)-1-[(5-chloro-1-

phenylsulfonylindol-2-yl)sulfonyl]-3-

[(methoxycarbonyl)methyl]piperazine (2.5 g), followed by the addition of lithium borohydride (135 mg). The resulting mixture was stirred for 48 hours. The solvent was distilled off under reduced pressure. Water and chloroform were then added to the reaction mixture and the mixture was separated into layers. The organic layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (ethyl acetate : hexane = 2:3), whereby the title compound (1.84 g) was obtained as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47(9H,s), 1.60(2H,m), 2.98-4.42(9H,m), 7.42-7.59(6H,m), 8.01(1H,d,J=1.2Hz), 8.03(1H,d,J=1.2Hz), 8.21(1H,d,J=9.3Hz).

MS (FAB) m/z: 584 [(M+H)<sup>+</sup>].

[Referential Example 440] 4-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-(formylmethyl)piperazine

In the same manner as in Referential Example 285, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45(9H,s), 2.64(1H,dd,J=5.4,17.4Hz), 2.95-3.15(5H,m), 3.72(1H,d,J=13.2Hz), 3.94(1H,m), 4.73(1H,m), 7.40-7.58(6H,m), 8.00(1H,d,J=1.2Hz), 8.02(1H,d,J=1.2Hz), 8.20(1H,d,J=9.0Hz), 9.62(1H,s).

[Referential Example 441] 4-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-[2-(1,4-dioxo-8-azaspiro[4,5]-decan-8-yl)ethyl]piperazine

In the same manner as in Referential Example 265, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45 (9H, s), 1.68 (4H, t,  $J=6.4\text{Hz}$ ), 1.83-3.20 (12H, m), 3.61 (1H, m), 3.94 (4H, s), 4.0-4.25 (2H, m), 7.39-7.58 (6H, m), 8.01 (1H, d,  $J=1.5\text{Hz}$ ), 8.04 (1H, d,  $J=1.0\text{Hz}$ ), 8.22 (1H, d,  $J=9.3\text{Hz}$ ).

MS (FAB)  $m/z$ : 709  $[(M+H)^+]$ .

[Referential Example 442] 4-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-[(1,3-dioxolan-2-yl)methyl]piperazine

In toluene (10 mL) were dissolved 4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-(formylmethyl)piperazine (440 mg) and ethylene glycol (71 mg), followed by the addition of  $p\text{-TsOH} \cdot \text{H}_2\text{O}$  (15 mg). The resulting mixture was heated to  $60^\circ\text{C}$  and stirred for 16 hours. Ethyl acetate was added to the reaction mixture.

The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous  $\text{MgSO}_4$  and distilled under reduced pressure to remove the solvent, whereby the title compound (460 mg) was obtained as colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45(9H,s), 1.63(2H,m), 1.98(2H,m), 2.49-3.95(3H,m), 3.66-4.13(8H,m), 4.78(1H,t,J=4.9Hz), 7.17(1H,m), 7.42-7.58(5H,m), 8.02(1H,d,J=1.5Hz), 8.04(1H,d,J=1.0Hz), 8.23(1H,d,J=9.3Hz).

5 MS (FAB) m/z: 626 [(M+H)<sup>+</sup>].

[Referential Example 443] 1,4-Dibenzyl-2-[(1,3-dioxoisindol-2-yl)methyl]piperazine

To a solution of 1,4-dibenzyl-2-(hydroxymethyl)piperazine (1.51 g), phthalimide (0.790 g)  
10 and triphenylphosphine (1.40 g) in tetrahydrofuran (20 ml) was added a 40% toluene solution (2.34 ml) of diethyl azodicarboxylate under ice cooling. The resulting mixture was stirred at room temperature for 6 hours. Furthermore, 1,4-dibenzyl-2-(hydroxymethyl)piperazine (0.87 g),  
15 phthalimide (0.486 g), triphenylphosphine (0.81 g) and tetrahydrofuran (5 ml) were added to the reaction mixture, followed by the addition of a 40% toluene solution (1.34 ml) of diethyl azodicarboxylate under ice cooling. The resulting mixture was stirred at room temperature for 18.5  
20 hours. Phthalimide (0.405 g) and a 40% toluene solution (1.10 ml) of diethyl azodicarboxylate were added under ice cooling, followed by stirring at room temperature for 20 hours. The solvent was distilled off under reduced pressure. The residue was subjected to column  
25 chromatography twice (3% methanol - methylene chloride for the first time and ethyl acetate / hexane = 1/3 for the

second time) using as a carrier silica gel, whereby a crude product was obtained. The crude product was crystallized from hexane - methylene chloride, collected by filtration and washed with hexane, whereby the title compound (0.243 g) was obtained as colorless powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.30-2.40 (4H,m), 2.50-2.60 (1H,m), 2.95-3.10 (2H,m), 3.40-3.55 (2H,m), 3.60-3.65 (1H,m), 3.75-3.80 (1H,m), 3.95-4.05 (1H,m), 4.15-4.25 (1H,m), 7.10-7.35 (10H,m), 7.70-7.75 (2H,m), 7.80-7.85 (2H,m).

MS (FAB)  $m/z$ : 426 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 444] 1-[(5-Chloro-1-phenylsulfonyl)piperazin-2-yl]-3-[(1,4-dioxoisindol-2-yl)methyl]piperazine

In the same manner as in Referential Example 266, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.77-2.88 (2H,m), 2.98-3.09 (2H,m), 3.16-3.18 (1H,m), 3.69-3.72 (3H,m), 3.81 (1H,broad d,  $J=12.6\text{Hz}$ ), 7.36 (1H,s), 7.40-7.46 (3H,m), 7.52-7.56 (2H,m), 7.71-7.74 (2H,m), 7.83-7.86 (2H,m), 7.99 (2H,dd,  $J=1.1, 7.4\text{Hz}$ ), 8.22 (1H,d,  $J=9.2\text{Hz}$ ).

MS (FAB)  $m/z$ : 599 [ $\text{M}+\text{H}$ ] $^+$ ,  $\text{Cl}^{35}$ ], 601 [ $\text{M}+\text{H}$ ] $^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 445] 1,4-Di(tert-butoxycarbonyl)-2-(2-phenoxyethyl)piperazine

To a solution of 1,4-di(tert-butoxycarbonyl)-2-(2-hydroxyethyl)piperazine (0.660 g, 2 mmol) and

triphenylphosphine (0.577 g, 2.2 mmol) in tetrahydrofuran (10 ml) were added a solution of phenol (0.188 g, 2 mmol) in tetrahydrofuran (5 ml) and diethyl azodicarboxylate (0.35 ml, 2.2 mmol), followed by stirring at room temperature for 4 hours. The reaction mixture was purified by flash column chromatography (ethyl acetate / n-hexane = 1/4) using as a carrier silica gel, whereby the title compound (0.611 g, 75%) was obtained as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.38(9H,s), 1.46(9H,s), 1.91-1.96(1H,m), 2.06-2.12(1H,m), 2.81-3.00(2H,broad), 3.94-3.98(6H,m), 4.40(1H,broad), 6.86(2H,d,J=7.8Hz), 6.92(1H,dd,J=7.2,7.2Hz), 7.23-7.27(2H,m).

MS (FAB) m/z: 407 (M+H)<sup>+</sup>.

[Referential Example 446] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(2-phenoxyethyl)piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.81-1.86(2H,m), 2.70-2.76(1H,m), 2.93-3.07(4H,m), 3.76-3.85(2H,m), 4.05(2H,t,J=5.8Hz), 6.84(2H,d,J=7.8Hz), 6.92-6.96(1H,m), 7.36(1H,s), 7.40-7.45(4H,m), 7.50-7.56(3H,m), 8.00(2H,d,J=7.5Hz), 8.22(1H,d,J=9.2Hz).

MS (FAB) m/z: 560 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 562 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 447] 1,4-Di(tert-butoxycarbonyl)-2-[2-(2-naphthoxy)ethyl]piperazine

In the same manner as in Referential Example 445, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.38(9H,s), 1.47(9H,s), 1.99-2.04(1H,m), 2.16(1H,m), 2.82-3.02(2H,broad), 4.00-4.12(6H,broad m), 4.46(1H,broad), 7.09-7.12(2H,m), 7.29-7.33(1H,m), 7.39-7.43(1H,m), 7.67-7.75(3H,m).  
MS (FAB)  $m/z$ : 457 ( $\text{M}+\text{H}$ ) $^+$ .

10 [Referential Example 448] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-(2-naphthoxy)ethyl]piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.89-1.95(2H,m), 2.73-2.79(1H,m), 2.92-3.09(4H,m), 3.79(1H,broad d,  $J=10.9\text{Hz}$ ), 3.87(1H,broad d,  $J=12.2\text{Hz}$ ), 4.18(2H,t,  $J=6.0\text{Hz}$ ), 7.06-7.10(2H,m), 7.31-7.35(1H,m), 7.36(1H,s), 7.39-7.48(5H,m), 7.52-7.56(1H,m), 7.69-7.72(2H,m), 7.76(1H,d,  $J=8.3\text{Hz}$ ), 8.00(2H,d,  $J=7.8\text{Hz}$ ),  
20 8.22(1H,d,  $J=9.2\text{Hz}$ ).

MS (FAB)  $m/z$ : 610 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 612 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 449] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-(tert-butyldiphenylsilyloxy)ethyl]piperazine



In the same manner as in Referential Example 266, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (9H, s), 1.55-1.61 (2H, m), 2.63-2.68 (1H, m), 2.88-3.01 (4H, m), 3.73-3.80 (4H, m), 7.33-7.45 (10H, m), 7.49-7.56 (2H, m), 7.61-7.64 (4H, m), 8.01 (2H, dd, J=1.1, 8.4 Hz), 8.22 (1H, d, J=9.3 Hz).

MS (FAB) m/z: 722 (M+H)<sup>+</sup>.

[Referential Example 450] 1-(tert-Butoxycarbonyl)-2-[2-(tert-butyl-diphenylsilyloxy)ethyl]-4-[(1-phenylsulfonyl-5-chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example 363, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (9H, s), 1.38 (9H, s), 1.84-1.92 (2H, m), 2.86-2.93 (1H, m), 3.02-3.14 (2H, m), 3.32 (1H, broad), 3.58-3.62 (2H, m), 3.92 (2H, broad d, J=12.4 Hz), 4.42 (1H, broad), 7.29 (1H, s), 7.32-7.43 (10H, m), 7.51-7.58 (5H, m), 7.99-8.01 (2H, m), 8.17 (1H, d, J=9.0 Hz).

MS (FAB) m/z: 822 (M+H)<sup>+</sup>.

[Referential Example 451] 1-(tert-Butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-(2-hydroxyethyl)piperazine

To a solution of 4-[(1-benzenesulfonyl-5-chloroindol-2-yl)sulfonyl]-1-(tert-butoxycarbonyl)-2-[2-(tert-butyl-diphenylsilyloxy)ethyl]piperazine (4.48 g) in tetrahydrofuran (20 ml) was added a 1.0M tetrahydrofuran solution (5.5 ml) of tetrabutylammonium fluoride, followed

by stirring at room temperature for 3.5 hours. After concentration under reduced pressure, the residue was purified by flash column chromatography (ethyl acetate : hexane = 1:9 to 1:0) using as a carrier silica gel, whereby the title compound (0.75 g) was obtained as a colorless solid.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.33(9H,s), 1.74-1.77(2H,m), 2.24-2.40(2H,m), 3.04(1H,m), 3.35-3.46(2H,m), 3.56-3.63(2H,m), 3.85-3.88(1H,broad d,  $J=13.2\text{Hz}$ ), 4.25(1H,broad), 4.43(1H,broad), 6.98(1H,d,  $J=0.7\text{Hz}$ ), 7.29(1H,dd,  $J=1.9, 8.8\text{Hz}$ ), 7.46-7.48(1H,m), 7.74(1H,m).

MS (FAB)  $m/z$ : 444 ( $M+H$ ) $^+$ .

[Referential Example 452] 1,4-Bis(tert-butoxycarbonyl)-2-(2-tosyloxyethyl)piperazine

A solution of 1,4-di(tert-butoxycarbonyl)-2-(2-hydroxyethyl)piperazine (5.05 g) and p-toluenesulfonyl chloride (4.34 g) in methylene chloride (200 ml) was cooled to 0°C, followed by the dropwise addition of triethylamine (11 ml). The resulting mixture was stirred at 0°C for 1 hour and at room temperature for 1 day. The reaction mixture was concentrated under reduced pressure. After dilution with ethyl acetate, the residue was washed with 1N hydrochloric acid, water and saturated aqueous NaCl solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate /

hexane = 1/4 to 1/1) using, as a carrier, silica gel, whereby the title compound (4.82 g) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.44 (18H, s), 1.78-1.84 (1H, m),  
5 1.94 (1H, broad), 2.44 (3H, s), 2.86 (3H, broad), 3.85 (2H, broad),  
3.97-4.07 (3H, m), 4.21 (1H, broad), 7.33 (2H, d,  $J=8.3\text{Hz}$ ),  
7.77 (2H, d,  $J=8.3\text{Hz}$ ).

MS (FAB)  $m/z$ : 485 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 453] 1,4-Bis(tert-butoxycarbonyl)-2-  
10 [2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

To a suspension of sodium hydride (60%, 57 mg) in N,N-dimethylformamide (20 ml), 2-oxazolidone (0.122 g) was added, followed by stirring at 90°C for 1 hour. A solution of 1,4-di(tert-butoxycarbonyl)-2-(2-  
15 tosyloxyethyl)piperazine (0.686 g) in N,N-dimethylformamide (15 ml) was added to the reaction mixture. The resulting mixture was stirred at 90°C for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate, washed with water  
20 and saturated aqueous NaCl solution, dried over magnesium sulfate and concentrated under reduced pressure, whereby the title compound (0.515 g) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.46 (8H, s), 1.47 (10H, s), 1.78-1.85 (2H, m),  
25 2.81-2.95 (3H, m), 3.39-3.64 (2H, m), 3.85-4.05 (2H, broad),

4.00 (2H, broad d,  $J=13.4$  Hz), 4.09-4.28 (2H, m), 4.30-4.34 (2H, m).

MS (FAB)  $m/z$ : 400  $(M+H)^+$ .

[Referential Example 454] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.51-1.76 (2H, m), 2.69-2.74 (1H, m), 2.77-2.85 (2H, m), 2.96-3.03 (2H, m), 3.20-3.27 (1H, m), 3.48-3.55 (2H, m), 3.59-3.69 (2H, m), 3.83 (1H, broad d,  $J=11.7$  Hz), 4.30-4.40 (2H, m), 7.39-7.46 (4H, m), 7.51-7.57 (2H, m), 7.99-8.02 (2H, m), 8.22 (1H, d,  $J=9.0$  Hz).

MS (FAB)  $m/z$ : 553  $[(M+H)^+, \text{Cl}^{35}]$ , 555  $[(M+H)^+, \text{Cl}^{37}]$ .

[Referential Example 455] 4,5-Bis(bromomethyl)thiazole

At room temperature, 4,5-dimethylthiazole (5.00 g), N-bromosuccinic imide (15.7 g) and  $\alpha, \alpha'$ -azobisisobutyronitrile (362 mg) were dissolved in ethylene dichloride (500 ml), followed by heating under reflux for 1 hour. After completion of the reaction, the solvent was distilled off and the residue was purified by chromatography on a silica gel column (hexane : diethyl ether = 1:4), whereby the title compound (5.24 g, 44%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.64 (2H, s), 4.74 (2H, s), 8.75 (1H, s).

[Referential Example 456] 5,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazine

Under ice cooling, 4,5-bis(bromomethyl)thiazole (600 mg) and 1,2-dimethylhydrazine dihydrochloride (294 mg) were suspended in ethanol (20 ml). Triethylamine (1.23 ml) was added in one portion to the reaction mixture, followed by stirring at room temperature for 30 minutes and then, at 50°C for 30 minutes. The solvent was distilled off and the residue was purified by chromatography on a silica gel column (5% methanol - methylene chloride), whereby the title compound (90 mg, 24%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.43(3H,s), 2.56(3H,s), 3.92(2H,s), 4.06(2H,br s), 8.68(1H,s).

MS (FAB) m/z: 170 (M+H)<sup>+</sup>.

[Referential Example 457] 3-(Methoxycarbonylmethyl)-1-[[1-phenylsulfonyl-5-(trimethylsilylethynyl)indol-2-yl]sulfonyl]piperazine

In the same manner as in Referential Example 226, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.25(9H,s), 2.38(1H,dd,J=16.2,8.8Hz), 2.46(1H,dd,J=16.2,4.2Hz), 2.76(1H,dd,J=12.5,10.0Hz), 2.91-2.99(1H,m), 2.99-3.07(2H,m), 3.17-3.25(1H,m), 3.67(3H,s), 3.69-3.78(2H,m), 7.38-7.44(3H,m), 7.54(1H,t,J=7.6Hz), 7.58(1H,dd,J=8.9,1.6Hz), 7.68(1H,d,J=1.6Hz), 7.98-8.02(2H,m), 8.22(1H,d,J=8.9Hz).

MS (FAB)  $m/z$ : 574 (M+H)<sup>+</sup>.

[Referential Example 458] 1,4-Bis(t-butoxycarbonyl)-2-[2-[(morpholin-4-yl)sulfonyl]ethyl]piperazine

In the same manner as in Referential Example 293, the  
5 title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.47(18H,s), 1.95-2.00(1H,m), 2.10-2.20(1H,m), 2.70-3.10(5H,m), 3.25(4H,t,J=4.7Hz), 3.75(4H,t,J=4.7Hz), 3.80-4.30(4H,m).

MS (FAB)  $m/z$ : 464 (M+H)<sup>+</sup>.

10 [Referential Example 459] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-[(morpholin-4-yl)sulfonyl]ethyl]piperazine

In the same manner as in Referential Example 220, the  
title compound was obtained.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.80-1.90(1H,m), 1.90-2.00(1H,m), 2.60-2.70(1H,m), 2.80-3.10(6H,m), 3.20-3.30(4H,m), 3.60-3.85(6H,m), 7.40-7.50(4H,m), 7.50-7.60(2H,m), 8.00-8.10(2H,m), 8.22(1H,d,J=9.1Hz).

MS (FAB)  $m/z$ : 617 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 619 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Referential Example 460]

1,4-Bis(tert-butoxycarbonyl)-2-hydroxymethylpiperazine

In the same manner as in Referential Example 284, the  
title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.46-1.47(18H,m), 2.70-4.400(10H).

[Referential Example 461] 1,4-Bis(tert-butoxycarbonyl)-2-formylpiperazine

In the same manner as in Referential Example 285, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45-1.50 (18H,m), 2.80-3.00 (1H,m), 3.00-3.20 (2H,m), 3.70-4.00 (2H,m), 4.40-4.70 (2H,m), 9.59 (1H,s).  
MS (FAB)  $m/z$ : 315 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 462] 1,4-Bis(tert-butoxycarbonyl)-2-(2-ethoxycarbonylethenyl)piperazine

10 In a 50-ml two-necked flask, sodium hydride (141 mg, 60% in oil) was charged, followed by purging with argon. Tetrahydrofuran (5 ml) was added and then, triethyl phosphonoacetate (700  $\mu\text{l}$ ) was added under ice cooling. The resulting mixture was stirred at room temperature for 15  
15 minutes. The reaction mixture was cooled again and under ice cooling, a solution of 1,4-bis(tert-butoxycarbonyl)-2-formylpiperazine (911 mg) dissolved in tetrahydrofuran (7 ml) was added dropwise, followed by stirring at room temperature for 4 hours. After completion of the reaction,  
20 water was added and then ethyl acetate was added, whereby the mixture was separated into layers. The organic layer thus obtained was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue  
25 was subjected to flash column chromatography (hexane : ethyl acetate = 2:1) using, as a carrier, silica gel,

whereby the title compound (920 mg, 83%) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20-1.30 (3H, m), 1.40-1.50 (18H, m), 2.75-3.20 (3H, m), 3.80-4.80 (6H, m), 5.93 (1H, dd,  $J=15.9, 2.0\text{Hz}$ ),  
5 6.82 (1H, dd,  $J=15.9, 4.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 385 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 463] 1,4-Bis(tert-butoxycarbonyl)-2-(2-ethoxycarbonylethyl)piperazine

10 In the same manner as in Referential Example 287, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.25 (3H, t,  $J=7.1\text{Hz}$ ), 1.46 (9H, s), 1.46 (9H, s), 1.70-1.85 (1H, m), 1.85-2.00 (1H, m), 2.20-2.40 (2H, m), 2.70-3.00 (3H, m), 3.80-4.20 (6H, m).

MS (FAB)  $m/z$ : 387 ( $\text{M}+\text{H}$ ) $^+$ .

15 [Referential Example 464] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(2-ethoxycarbonylethyl)piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.25 (3H, t,  $J=7.2\text{Hz}$ ), 1.30-1.80 (3H, m), 2.30-2.45 (2H, m), 2.55-2.65 (1H, m), 2.75-3.05 (4H, m), 3.70-3.80 (2H, m), 4.11 (2H, q,  $J=7.2\text{Hz}$ ), 7.35-7.50 (4H, m), 7.50-7.60 (2H, m), 8.02 (2H, d,  $J=7.3\text{Hz}$ ), 8.22 (1H, d,  $J=9.3\text{Hz}$ ).

MS (FAB)  $m/z$ : 540 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 542 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].



[Referential Example 465] 1,4-Bis(tert-butoxycarbonyl)-2-(2-cyanoethyl)piperazine

To an aqueous solution (3.0 ml) of potassium cyanide (85.0 mg) was added a solution of 1,4-bis(t-butoxycarbonyl)-2-(2-bromoethyl)piperazine (393 mg) in ethanol (3.0 ml), followed by stirring under heat at 110°C for 3 hours. After the removal of ethanol by distillation under reduced pressure, methylene chloride (100 ml) was added to the residue. The organic layer was washed with distilled water until the water phase became neutral. The resulting organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (silica gel 15 g, hexane : ethyl acetate = 2:1), whereby the title compound (145.0 mg, 43%) was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47(12H,s), 1.49(6H,s), 1.75-1.88(1H,m), 1.92-2.10(1H,m), 2.28-2.35(2H,m), 2.70-3.10(3H,m), 3.80-4.15(3H,m), 4.20-4.30(1H,m).

MS (FAB) m/z: 340 (M+H)<sup>+</sup>.

[Referential Example 466] 4-[(1-Phenylsulfonyl-5-chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.65-1.77(1H,m), 1.78-1.90(1H,m), 2.48(2H,t,J=7.6Hz), 2.70(1H,dd,J=12.5,9.5Hz), 2.85-

3.10 (4H,m), 3.62-3.70 (1H,m), 3.75-3.85 (1H,m), 7.40-  
7.50 (4H,m), 7.55-7.60 (2H,m), 8.01 (2H,dd,J=8.6,1.2Hz),  
8.22 (1H,d,J=9.0Hz).

MS (FAB) m/z: 493 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 495 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Referential Example 467] 2-Amino-6,6-ethylenedioxy-  
4,5,6,7-tetrahydrobenzo[d]thiazole

In a 200-ml egg-plant type flask, 1,4-cyclohexanedione  
ethylene ketal (7.80 g) was charged and dissolved in  
cyclohexane (20 mL). To the resulting solution were added  
10 pyrrolidine (4.35 mL) and p-toluenesulfonic acid  
monohydrate (48.0 g), followed by heating under reflux  
while water was trapped by a Dean and Stark apparatus.  
After 70 minutes, the reaction mixture was cooled to room  
temperature and the solvent was decanted and concentrated  
15 under reduced pressure. The residue was dissolved in  
methanol (15 ml). While attention was paid so as not to  
occur a temperature rise due to water bath, sulfur powder  
(1.60 g) was added to the resulting solution. After 15  
minutes, a solution of cyanamide (2.10 g) in methanol (10  
20 mL) was added dropwise over 20 minutes. After 14 hours,  
the solvent was distilled off under reduced pressure. The  
residue was subjected to chromatography on a silica gel  
column (silica gel: 300 g, methylene chloride : methanol =  
100:5 → 10:1), whereby the title compound (8.89 g) was  
25 obtained as a dark green solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.96(2H,t,J=6.4Hz), 2.74(2H,t,J=6.4Hz),  
2.81(2H,s), 4.02(4H,s), 4.77(2H,br s).

MS (FAB)  $m/z$ : 213 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 468] 2-Chloro-6,6-ethylenedioxy-

5 4,5,6,7-tetrahydrobenzo[d]thiazole

Copper (II) chloride (760 mg) was charged in a 100-mL egg-plant type flask and dissolved in acetonitrile (10 mL). While cooling over water bath, tert-butyl nitrite (730 mg) was added in one portion to the resulting solution. After  
10 10 minutes, 2-amino-6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazole (1.00 g) was added over about 50 minutes, followed by stirring at room temperature for 1 hour. The reaction mixture was then heated to 65°C and stirring was continued for 2 hours. After silica gel (5 g)  
15 was added to the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (silica gel: 50 g, hexane : ethyl acetate = 3:1), whereby the title compound (860 mg) was obtained as a yellow oil.

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.00(2H,t,J=6.4Hz), 2.91(4H,m),  
4.03(4H,s).

MS (FAB)  $m/z$ : 232 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 234 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 469] 6,6-Ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazole

In a 100-mL egg-plant type flask, 2-chloro-6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazole (860 mg) was charged and was dissolved in methanol (10 mL). To the resulting solution were added 10% palladium-carbon (100 mg) and sodium acetate (305 mg), followed by stirring under a hydrogen gas stream of 4.5 atmospheric pressure. After 17 hours, palladium was filtered off and the solvent was distilled off under reduced pressure. The residue was subjected to chromatography on a silica gel column (silica gel: 50 g, ethyl acetate : hexane = 1:1), whereby the title compound (720 mg) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.04 (2H, t,  $J=6.8\text{Hz}$ ), 3.03 (4H, m), 4.05 (4H, s), 8.62 (1H, s).

MS (FAB)  $m/z$ : 198 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 470] Lithium (6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)carboxylate

In the same manner as in Referential Example 371, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ : 1.94 (2H, t,  $J=6.6\text{Hz}$ ), 3.34-3.44 (4H, m), 3.95 (4H, s).

[Referential Example 471] 2-Amino-4,5-dihydro-7H-pyrano[4,3-d]thiazole

In the same manner as in Referential Example 467, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.66-2.70 (2H,m), 3.97 (2H,t,J=5.6Hz),  
4.63 (2H,s), 4.94 (2H,br s).

MS (FAB) m/z: 157 (M+H)<sup>+</sup>.

[Referential Example 472] 2-Chloro-4,5-dihydro-7H-  
5 pyrano[4,3-d]thiazole

In the same manner as in Referential Example 468, the  
title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.85-2.89 (2H,m), 4.02 (2H,t,J=5.6Hz),  
4.73 (2H,s).

10 MS (FAB) m/z: 175 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 177 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 473] 4,5-Dihydro-7H-pyrano[4,3-  
d]thiazole

In the same manner as in Referential Example 469, the  
title compound was obtained.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.97-3.01 (2H,m), 4.04 (2H,t,J=5.6Hz),  
4.87 (2H,s), 8.69 (1H,s).

MS (FAB) m/z: 142 (M+H)<sup>+</sup>.

[Referential Example 474] Lithium (4,5-dihydro-7H-  
pyrano[4,3-d]thiazol-2-yl)carboxylate

20 In a 200-mL three-necked flask, 4,5-dihydro-7H-  
pyrano[4,3-d]thiazole (1.14 g) was added and dissolved in  
ether (30 mL). After cooling to -78°C, 1.6M butyl lithium  
(6.6 mL) was added and the resulting mixture was stirred.  
After 20 minutes, a carbon dioxide gas was introduced.

25 After about 15 minutes, the introduction was terminated.

The reaction mixture was allowed to rise back to room temperature and concentrated under reduced pressure, whereby the title compound (1.65 g) was obtained as a colorless amorphous substance.

5  $^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.83 (2H, t,  $J=5.6\text{Hz}$ ), 3.92 (2H, t,  $J=5.6\text{Hz}$ ), 4.73 (2H, s).

[Referential Example 475] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(phenylsulfonyl)carbamoyl]methyl]piperazine  
10 trifluoroacetate

In tetrahydrofuran (10 ml) was dissolved 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (1.00 g), followed by the addition of carbonyldiimidazole (1.06 g). The resulting mixture was  
15 heated overnight under reflux. After cooling to room temperature, the reaction mixture was added with benzenesulfonamide (685 mg), 1,8-diazabicyclo[5.4.0]-7-undecene (0.64 ml) and carbonyldiimidazole (353 mg). The resulting mixture was heated under reflux for 1 hour. The  
20 reaction mixture was then concentrated under reduced pressure. Dichloromethane was added to the residue and the solid thus precipitated was filtered off. The filtrate was washed successively with 1N hydrochloric acid and saturated aqueous NaCl solution. The organic layer was dried over  
25 anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column ( $\Phi$  3.0 x 10.0 cm, dichloromethane : methanol = 100:1), whereby pale brown foam was obtained. The resulting foam was dissolved in dichloromethane (10 ml), followed by the addition of trifluoroacetic acid (10 ml). After stirring at room temperature for 1 minute, the reaction mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the resulting precipitate was collected by filtration, whereby the title compound (496 mg, 31%) was obtained as colorless foam.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.60-2.75 (3H,m), 3.10-3.20 (1H,m), 3.29-3.38 (1H,m), 3.53-3.73 (4H,m), 7.06 (1H,d,J=2.0Hz), 7.34 (1H,dd,J=8.8,2.0Hz), 7.50 (1H,d,J=8.8Hz), 7.64 (2H,t,J=7.1Hz), 7.74 (1H,t,J=7.1Hz), 7.80 (1H,d,J=2.0Hz), 7.93 (2H,d,J=7.1Hz), 12.53 (1H,s).

MS (FAB)  $m/z$ : 497 [(M+H) $^+$ , Cl $^{35}$ ], 499 [(M+H) $^+$ , Cl $^{37}$ ].

[Referential Example 476] 1-tert-Butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(N-methylsulfonylcarbonyl)methyl]piperazine

In tetrahydrofuran (10 ml) was dissolved 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (1.00 g), followed by the addition of carbonyldiimidazole (1.06 g). The resulting mixture was heated overnight under reflux. After cooling to room temperature, methanesulfonamide (415 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.64 ml) were added,

followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. Dichloromethane was added to the residue and the resulting mixture was washed successively with 1N hydrochloric acid, and saturated aqueous NaCl solution. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column ( $\Phi$  3.0 x 10.0 cm, dichloromethane : methanol = 100:1), whereby the title compound (518 mg, 44%) was obtained as colorless foam.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.33(9H,s), 2.23-2.60(3H,m), 2.62-2.78(1H,m), 3.05(1H,br s), 3.21(3H,s), 3.52-3.70(2H,m), 3.84-3.97(1H,m), 4.56(1H,br s), 7.02(1H,s), 7.32(1H,d,J=8.8Hz), 7.49(1H,J=8.8Hz), 7.77(1H,s), 11.84(1H,s), 12.43(1H,s).

MS (FAB)  $m/z$ : 557  $[(M+Na)^+, Cl^{35}]$ , 559  $[(M+Na)^+, Cl^{37}]$ .

[Referential Example 477] 1-[(5-Chloroindol-2-yl)sulfonyl]-3-[(N-methyl-N-

methylsulfonylcarbamoyl)methyl]piperazine trifluoroacetate

In N,N-dimethylformamide (10 ml) was dissolved 1-tert-butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(N-methylsulfonylcarbamoyl)methyl]piperazine (347 mg), followed by the addition of sodium bicarbonate (55 mg) and methyl iodide (0.05 ml). The resulting mixture was stirred overnight at room temperature. The reaction mixture was



then concentrated under reduced pressure. Dichloromethane was added to the residue and the resulting mixture was washed successively with water and saturated aqueous NaCl solution, each once. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column ( $\Phi$  1.7 x 12.0 cm, dichloromethane : methanol = 200:1), whereby the title compound was obtained as colorless foam. The resulting foam was dissolved in dichloromethane (1 ml), followed by the addition of trifluoroacetic acid (2 ml). After the resulting mixture was stirred at room temperature for 1 minute, the reaction mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the precipitate so formed was collected by filtration, whereby the title compound (189 mg, 43%) was obtained as colorless foam.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.60-2.80 (2H,m), 3.02-3.11 (2H,m), 3.16 (3H,s), 3.20-3.30 (1H,m), 3.39 (3H,s), 3.61-3.80 (4H,m), 7.08 (1H,d,J=1.5Hz), 7.34 (1H,dd,J=8.8,2.0Hz), 7.50 (1H,J=8.8Hz), 7.80 (1H,d,J=2.2Hz), 12.54 (1H,br s).  
 $\text{MS (FAB) m/z}$ : 449  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 451  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 478] N-methanesulfonylhydrazine hydrochloride

In pyridine (30 ml) was dissolved t-butyl carbazate (2.64 g), followed by the addition of methanesulfonyl chloride (1.62 ml) under ice cooling. The resulting mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed successively with 1N hydrochloric acid and a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was solidified by the addition of hexane and ethyl acetate, whereby a pale yellow solid was obtained. The solid was dissolved in dichloromethane (20 ml), followed by the addition of saturated solution of hydrochloride in ethanol (20 ml). The resulting mixture was then concentrated under reduced pressure. The residue was solidified by the addition of ethyl acetate, whereby N-methanesulfonylhydrazine (1.67 g, 57%) was obtained as a pale yellow solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.25(3H,s), 9.80(br s,9.80).

MS (FAB)  $m/z$ : 111 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 479] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(2-methylsulfonylhydrazino)carbonylmethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

In dichloromethane (20 ml) were dissolved 1-tert-butoxycarbonyl-2-carboxymethyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (600 mg), N-methanesulfonylhydrazine (192 mg), 1-hydroxybenzotriazole monohydrate (200 mg) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (301 mg), followed by the addition of triethylamine (0.21 ml). The resulting mixture was stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed with water and saturated aqueous NaCl solution, each once. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column ( $\Phi$  3.0 x 8.0 cm, dichloromethane : methanol = 50:1), whereby colorless foam was obtained. The resulting foam was dissolved in dichloromethane (2 ml), followed by the addition of trifluoroacetic acid (10 ml). After the resulting mixture was stirred at room temperature for 1 minute, the reaction mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the precipitate so formed was collected by filtration, whereby the title compound (278 mg, 38%) was obtained as colorless foam.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.51-2.82 (3H,m), 2.96 (3H,s), 3.11-3.21 (1H,m), 3.31-3.42 (1H,m), 3.60-3.85 (4H,m), 7.07 (1H,s),

7.34 (1H, dd, J=8.8, 2.0 Hz), 7.50 (1H, J=8.8 Hz), 7.80 (1H, s),  
 9.52 (1H, d, J=2.7 Hz), 10.39 (1H, d, J=2.7 Hz), 12.51-12.57 (1H, m).  
 MS (FAB) m/z: 450 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 452 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 480] 1-(tert-Butoxycarbonyl)-4-[(5-  
 5 chloroindol-2-yl)sulfonyl]-2-[(pyrrolidin-1-  
 ylcarbonyl)methyl]piperazine

The title compound was obtained by employing the  
 method of Referential Example 319 in which 1-(3-  
 dimethylaminopropyl-3-ethylcarbodiimide hydrochloride had  
 10 been used as a condensing agent.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (9H, s), 1.85-1.97 (2H, m), 1.98-  
 2.18 (2H, m), 2.22-2.35 (1H, m), 2.50-3.00 (3H, m),  
 2.97 (1H, dt, J=3.4, 13.0 Hz), 3.40-3.60 (4H, m), 3.64-3.75 (1H, m),  
 3.80-4.20 (2H, m), 4.63 (1H, br d, J=10.0 Hz),  
 15 6.96 (1H, d, J=1.7 Hz), 7.27 (1H, dd, J=9.1, 1.7 Hz),  
 7.37 (1H, d, J=9.1 Hz), 7.65 (1H, d, J=1.7 Hz).

MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 481] 2-[(N-Benzylcarbonyl)methyl]-1-  
 (tert-butoxycarbonyl)-4-[(5-chloroindol-2-  
 20 yl)sulfonyl]piperazine

The title compound was obtained by employing the  
 method of Referential Example 319 in which 1-(3-  
 dimethylaminopropyl-3-ethylcarbodiimide hydrochloride had  
 been used as a condensing agent.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40 (9H, s), 2.35-2.48 (1H, m), 2.50-2.85 (3H, m), 2.95-3.07 (1H, m), 3.62-3.78 (1H, m), 3.80-4.15 (2H, m), 4.40-4.50 (2H, m), 4.60-4.70 (1H, m), 6.93 (1H, s), 7.20-7.40 (7H, m), 7.64 (1H, s).

5 MS (FAB)  $m/z$ : 547  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 549  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 482] 5(6)-chloro-2-mercaptobenzimidazole

Carbon disulfide (6.60 ml) and sodium hydroxide (6.330 g) were added to the mixture of 4-chloro-1,2-phenylenediamine (14.37 g), ethanol (100 ml) and water (15 ml), and reacted under reflux for 3 hours. The reaction mixture was added by active carbon (4.0 g), refluxed for 10 minutes, and filtrated by means of suction. The precipitated substances were washed with ethanol (100 ml) and 70°C hot water (200 ml) to obtain a solution. The obtained solution was added to the mixture of acetic acid (9.0 ml) and water (16.0 ml), concentrated under reduced pressure, purified by chromatography on a silica gel column (ethyl acetate), and solidified by acetone-water and ethyl acetate-hexane, followed by drying. Thus, the title compound (9.03 g) was obtained as pale yellow powder.

m.p. >220°C (dec)

IR (KBr)  $\text{cm}^{-1}$  3116, 3084, 3055, 2952, 1614, 1512, 1475, 1369, 1323, 1190, 1066.

25  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  7.15 (2H, s), 7.21 (1H, s).

MS (EI)  $m/z$  184 [ $M^+$ ,  $C^{135}$ ], 186 [ $M^+$ ,  $C^{137}$ ].

[Referential Example 483] 1-(tert-butoxycarbonyl)-4-  
[[5(6)-chlorobenzimidazol-2-yl]sulfonyl]piperazine

5(6)-chloro-2-mercaptobenzimidazole (1.837 g) was  
5 suspended in a 20% solution of acetic acid, and then blown  
by a chloride gas at a temperature less than  $7^{\circ}\text{C}$  for 70  
minutes. Yellow precipitates were obtained by filtration  
and thereafter, washed with cold water. The obtained  
yellow solid was added to the mixture of 1-(tert-  
10 butoxycarbonyl)piperazine (3.905 g), water (18 ml) and  
acetone (20 ml), and stirred at room temperature for 20  
hours. After discarding the acetone, precipitates were  
filtered and dried, whereby the title compound (3.16 g) was  
obtained as pale yellow powder.

15 m.p.  $210-211^{\circ}\text{C}$

IR (KBr)  $\text{cm}^{-1}$  3212, 2983, 1666, 1435, 1367, 1356, 1279,  
1176, 1165, 1147, 1138, 974, 949.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.44 (9H, s), 3.33-3.41 (4H, m), 3.53-3.59  
(4H, m), 7.30-7.60 (2H, m), 7.72-7.88 (1H, m).

20 MS (FAB)  $m/z$  401 [ $(M^+ + H)^+$ ,  $C^{135}$ ], 403 [ $(M^+ + H)^+$ ,  $C^{137}$ ].

[Referential Example 484] 1-[[5(6)-chlorobenzimidazol-2-  
yl]sulfonyl]piperazine hydrochloride

Saturated solution of hydrochloride in ethanol (5.0  
ml) was added to the mixture of 1-(tert-butoxycarbonyl)-4-  
25 [[5(6)-chlorobenzimidazol-2-yl]sulfonyl]piperazine (1.406

g), ethanol (5.0 ml) and dichloromethane (4.0 ml), and then stirred at room temperature for 4 hours. After concentration under reduced pressure, the obtained product was purified by chromatography on a silica gel column (dichloromethane:methanol = 20:1). The purified compound was added to 1N solution of hydrochloride in ethanol (1 ml), concentrated and dried, whereby the title compound (1.19 g) was obtained as a hygroscopic colorless amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 3.25-3.80 (8H, m), 7.40-7.50 (1H, br), 7.60-7.80 (2H, br), 9.20-9.55 (1H, br).

MS (FAB) m/z 301 [(M + H)<sup>+</sup>, C<sup>135</sup>], 303 [(M + H)<sup>+</sup>, C<sup>137</sup>].

[Example A-1] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

At room temperature, 1-[4-(4-pyridyl)benzoyl]piperazine ditrifluoroacetate (1.19 g) was suspended in dichloromethane (100 ml), followed by the addition of diisopropylethylamine (1.68 ml) and 6-chloro-2-naphthylsulfonyl chloride (WO/96/10022) (691 mg). After stirring at room temperature for 2 hours, the reaction mixture was purified by chromatography on a silica gel column (2% methanol - dichloromethane). To the resulting fraction, 1N hydrochloric acid in ethanol was added to make it weakly acidic. The solvent was then distilled off. The resulting colorless solid was washed with tetrahydrofuran,

whereby the title compound (1.05 g, 81%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.95-3.25 (4H, m), 3.43 (2H, br s),  
 3.60 (2H, br s), 7.56 (2H, d,  $J=8.3\text{Hz}$ ), 7.74 (1H, dd,  $J=8.8, 2.5\text{Hz}$ ),  
 5 7.83 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.01 (2H, d,  $J=8.3\text{Hz}$ ),  
 8.19 (1H, d,  $J=8.8\text{Hz}$ ), 8.25-8.40 (4H, m), 8.51 (1H, s),  
 8.94 (2H, d,  $J=6.8\text{Hz}$ ).

MS (FAB)  $m/z$ : 492  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 494  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_3\text{ClS}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$

10 Calculated: C, 58.10; H, 4.50; N, 7.82; Cl, 13.19; S, 5.97.

Found: C, 58.12; H, 4.67; N, 7.66; Cl, 13.12; S, 6.10.

[Example A-2] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

15 In dichloromethane (30 ml), 4-tert-butoxycarbonyl-2-ethoxycarbonyl-1-[4-(4-pyridyl)benzoyl]piperazine (514 mg) was dissolved, followed by the addition of trifluoroacetic acid (30 ml) under ice cooling. After stirring at room temperature for 45 minutes, the residue obtained by  
 20 distilling off the solvent was suspended in dichloromethane (100 ml) under ice cooling, followed by the addition of diisopropylethylamine (1.02 ml) and 6-chloro-2-naphthylsulfonyl chloride (W096/10022) (366 mg). After stirring at room temperature for one hour, the reaction  
 25 mixture was purified as was by chromatography on a silica gel column (1% methanol - dichloromethane). To the



resulting fraction, 1N hydrochloric acid in ethanol was added to make it weakly acidic. The solvent was then distilled off. The resulting colorless solid was washed with ethanol, whereby the title compound (308 mg, 43%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.15-1.30 (3H,m), 2.60-5.40 (9H,m), 7.50 (2/3H,d,J=8.3Hz), 7.57 (4/3H,d,J=7.8Hz), 7.74 (1H,dd,J=9.0,1.7Hz), 7.83 (1H,d,J=8.8Hz), 8.00 (2/3H,d,J=7.8Hz), 8.04 (4/3H,d,J=8.3Hz), 8.19 (1H,d,J=8.8Hz), 8.25-8.35 (4H,m), 8.55 (1H,s), 8.92 (2H,d,J=4.9Hz).

MS (FAB)  $m/z$ : 564  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 566  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{29}\text{H}_{26}\text{N}_3\text{O}_5\text{ClS}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 57.15; H, 4.63; N, 6.89; Cl, 11.63; S, 5.26.

Found: C, 56.95; H, 4.68; N, 6.70; Cl, 11.36; S, 5.30.

[Example A-3]

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine-2-carboxylic acid hydrochloride

In a mixed solvent of ethanol (1 ml), tetrahydrofuran (1 ml) and water (1 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride (152 mg) obtained in Example A-2 was dissolved under ice cooling, followed by the dropwise addition of a 1N aqueous solution of sodium hydroxide. The reaction mixture was stirred at room temperature for 90 minutes. After concentration under

reduced pressure, 1N hydrochloric acid was added to the reaction mixture to make it weakly acidic. The colorless solid so precipitated was collected by filtration, followed by drying, whereby the title compound (62 mg, 42%) was  
 5 obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.65-5.30 (7H, m), 7.49 (4/5H, d,  $J=7.7\text{Hz}$ ), 7.56 (6/5H, d,  $J=8.3\text{Hz}$ ), 7.74 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.82 (1H, d,  $J=8.3\text{Hz}$ ), 7.95-8.05 (2H, m), 8.19 (1H, d,  $J=8.3\text{Hz}$ ), 8.20-8.35 (4H, m), 8.53 (1H, s), 8.92 (2H, d,  $J=5.4\text{Hz}$ ).

10 MS (FAB)  $m/z$ : 536  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 538  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{27}\text{H}_{22}\text{N}_3\text{O}_5\text{ClS}\cdot 0.9\text{HCl}\cdot 1.2\text{H}_2\text{O}$

Calculated: C, 54.92; H, 4.32; N, 7.12; Cl, 11.41; S, 5.43.

Found: C, 54.94; H, 4.42; N, 6.83; Cl, 11.31; S, 5.33.

[Example A-4]

15 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)nicotinyll]piperazine hydrochloride

In dichloromethane (10 ml), 6-(4-pyridyl)nicotinic acid hydrochloride (96 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (150 mg) were  
 20 suspended, followed by the addition of 1-hydroxybenzotriazole (48 mg) and N-methylmorpholine (155  $\mu\text{l}$ ). After the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (102 mg) under ice cooling, the resulting mixture was stirred at room temperature for  
 25 16 hours. Owing to the slow reaction, N,N-dimethylformamide (10 ml) was added to the reaction mixture

and the resulting mixture was stirred for 3 days. After completion of the reaction, the solvent was distilled off. The residue was purified by chromatography on a silica gel column (1% methanol - dichloromethane). The solvent was then distilled off. To the residue, tetrahydrofuran and 1N hydrochloric acid in ethanol were added and the solid so precipitated was collected by filtration and dried, whereby the title compound (105 mg, 55%) was obtained as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.00-3.25(4H,m), 3.46(2H,br s), 3.76(2H,br s), 7.74(1H,dd,J=8.5,1.7Hz), 7.83(1H,d,J=8.8Hz), 8.07(1H,dd,J=7.8,1.5Hz), 8.19(1H,d,J=8.8Hz), 8.28(1H,s), 8.29(1H,d,J=8.8Hz), 8.42(1H,d,J=8.3Hz), 8.51(1H,s), 8.65(2H,d,J=6.4Hz), 8.80(1H,m), 9.01(2H,d,J=5.9Hz).  
MS (FAB) m/z: 493 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 495 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>21</sub>N<sub>4</sub>O<sub>3</sub>ClS·HCl·H<sub>2</sub>O

Calculated: C, 54.85; H, 4.42; N, 10.23; Cl, 12.95; S, 5.86.

Found: C, 54.57; H, 4.51; N, 10.06; Cl, 13.08; S, 5.87.

[Example A-5] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 4-(3-pyridyl)benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

trifluoroacetate as starting materials, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.00-3.25 (4H, m), 3.47 (2H, br s),  
3.73 (2H, br s), 7.51 (2H, d,  $J=8.3\text{Hz}$ ), 7.73 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
5 7.8-7.9 (3H, m), 7.92 (1H, dd,  $J=7.8, 5.4\text{Hz}$ ), 8.19 (1H, d,  $J=8.8\text{Hz}$ ),  
8.25-8.30 (2H, m), 8.50 (1H, s), 8.55-8.65 (1H, m), 8.75-  
8.85 (1H, m), 9.14 (1H, d,  $J=2.0\text{Hz}$ ).

MS (FAB)  $m/z$ : 492  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 494  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_3\text{ClS}\cdot 0.85\text{HCl}\cdot \text{H}_2\text{O}$

10 Calculated: C, 57.72; H, 4.63; N, 7.77; Cl, 12.12; S, 5.93.

Found: C, 57.44; H, 4.62; N, 7.68; Cl, 11.99; S, 5.83.

[Example A-6] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In dichloromethane (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (300 mg)  
15 obtained in Example A-1 was dissolved, followed by the addition of 3-chloroperbenzoic acid (382 g) at  $-20^\circ\text{C}$ . The resulting mixture was stirred at  $-20^\circ\text{C}$  for 21 hours. An aqueous solution of sodium sulfite was added to decompose  
20 an excess peroxide. Dichloromethane and a saturated aqueous solution of sodium bicarbonate were added to separate an organic layer. After drying the organic layer over anhydrous magnesium sulfate, the residue obtained by distilling off the solvent was purified by chromatography  
25 on a silica gel column (2-5% methanol - dichloromethane). After the solvent was distilled off, ether was added to the

residue to solidify it, followed by collection through filtration, whereby the title compound (200 mg, 63%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.90-3.40 (4H,m), 3.40-4.20 (4H,m),  
 5 7.43 (2H,d,J=8.3Hz), 7.47 (2H,d,J=7.3Hz), 7.55-7.65 (3H,m),  
 7.76 (1H,dd,J=8.8,1.5Hz), 7.90-8.00 (3H,m),  
 8.26 (2H,d,J=7.3Hz), 8.31 (1H,s).

MS (FAB)  $m/z$ : 508  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 510  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_4\text{ClS}\cdot 0.8\text{H}_2\text{O}$

10 Calculated: C, 59.78; H, 4.55; N, 8.04; Cl, 6.79; S, 6.14.

Found: C, 59.82; H, 4.45; N, 7.94; Cl, 6.85; S, 6.29.

[Example A-7] 1-[4-(2-Aminopyridin-5-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In a mixed solvent of dichloromethane (1 ml) and  
 15 ethanol (1 ml), 1-[4-[2-tert-butoxycarbonylamino]pyridin-5-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (128 mg) was dissolved, followed by the addition of a saturated hydrochloride solution in ethanol (10 ml) under ice cooling. After stirring at room temperature for 1  
 20 minute, the solvent was distilled off. Isopropanol was added to the residue for crystallization. The crystals so obtained were collected by filtration and dried, whereby the title compound (88 mg, 68%) was obtained as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.00-3.20 (4H,m), 3.30-3.90 (4H,m),  
 7.05 (1/2H,d,J=8.8Hz), 7.06 (1/2H,d,J=8.8Hz),  
 7.43 (2H,d,J=8.3Hz), 7.67 (2H,d,J=8.3Hz), 7.73 (1H,d,J=8.3Hz),  
 7.82 (1H,d,J=8.8Hz), 7.90-8.10 (2H,br), 8.18 (1H,d,J=8.3Hz),  
 8.25-8.35 (4H,m), 8.50 (1H,s).

MS (FAB) m/z: 507 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 509 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>3</sub>S·HCl·1.2H<sub>2</sub>O·0.8iPrOH

Calculated: C, 55.56; H, 5.52; N, 9.13; Cl, 11.55; S, 5.22.

Found: C, 55.40; H, 5.24; N, 8.85; Cl, 11.79; S, 5.50.

[Example A-8] 1-[4-(4-Aminophenyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-7, a reaction was conducted using 1-[4-[4-(tert-butoxycarbonylamino)phenyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material, whereby the title compound was obtained as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-3.20 (4H,m), 3.25-3.80 (4H,m),  
 6.68 (2H,d,J=8.3Hz), 7.32 (2H,d,J=8.3Hz), 7.39 (2H,d,J=8.3Hz),  
 7.54 (2H,d,J=8.3Hz), 7.73 (1H,dd,J=8.8,2.0Hz),  
 7.82 (1H,dd,J=8.8,2.0Hz), 8.18 (1H,dd,J=8.8Hz), 8.25-8.40 (2H,m), 8.50 (1H,br s).

MS (FAB) m/z: 506 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 508 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>3</sub>S·0.2HCl

Calculated: C, 63.18; H, 4.75; N, 8.19; Cl, 8.29; S, 6.25.

Found: C, 62.93; H, 4.93; N, 7.91; Cl, 7.99; S, 6.36.

[Example A-9] 1-[4-(2-Aminothiazol-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was effected using 4-(2-aminothiazol-4-yl)benzoic acid and 1-  
 5 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-3.20 (4H,m), 3.30-3.90 (4H,m),  
 7.26 (1H,s), 7.41 (2H,d,J=8.3Hz), 7.73 (1H,dd,J=8.8,2.0Hz),  
 10 7.79 (2H,d,J=8.3Hz), 7.82 (1H,dd,J=8.8,2.0Hz),  
 8.18 (1H,d,J=8.8Hz), 8.25-8.30 (2H,m), 8.50 (1H,br s).  
 MS (FAB) m/z: 513 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 515 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>21</sub>N<sub>4</sub>O<sub>3</sub>ClS<sub>2</sub>·HCl·0.3H<sub>2</sub>O

Calculated: C, 51.95; H, 4.11; N, 10.10; Cl, 12.78; S,  
 15 11.56.

Found: C, 51.99; H, 4.19; N, 10.03; Cl, 12.61; S,  
 11.45.

[Example A-10] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[imidazol-4(5)-yl]benzoyl]piperazine hydrochloride

20 In dichloromethane (5 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-[1-triphenylmethyylimidazol-4(5)-yl]benzoyl]piperazine (303 mg) was dissolved, followed by the addition of a saturated hydrochloride solution in ethanol (30 ml) under ice cooling. After stirring at room  
 25 temperature for 3 hours, the solvent was distilled off.  
 Ether was added to the residue for crystallization and the

resulting crystals were collected by filtration, whereby the title compound (307 mg, 76%) was obtained as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-3.20 (4H,m), 3.30-3.90 (4H,m),  
 5 7.47 (2H,d,J=8.3Hz), 7.74 (1H,dd,J=8.8,2.0Hz),  
 7.82 (1H,dd,J=8.8,2.0Hz), 7.89 (2H,d,J=8.3Hz),  
 8.19 (1H,d,J=8.8Hz), 8.22 (1H,d,J=1.0Hz), 8.25-8.30 (2H,m),  
 8.50 (1H,m), 9.22 (1H,d,J=1.0Hz).

MS (FAB) m/z: 481 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 483 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 Elementary analysis for C<sub>24</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>3</sub>S·HCl·0.4H<sub>2</sub>O

Calculated: C, 54.94; H, 4.38; N, 10.68; Cl, 13.52; S, 6.11.

Found: C, 54.98; H, 4.29; N, 10.62; Cl, 13.56; S, 6.14.

15 [Example A-11] 1-[4-(2-Aminoimidazol-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 4-[2-aminoimidazol-4-yl]benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials,  
 20 whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-3.20 (4H,m), 3.30-3.90 (4H,m),  
 7.39 (2H,d,J=8.3Hz), 7.47 (1H,s), 7.49 (2H,br s),  
 7.67 (2H,d,J=8.3Hz), 7.73 (1H,dd,J=8.8,2.5Hz),



7.82 (1H, dd, J=8.8, 2.0 Hz), 8.18 (1H, d, J=8.8 Hz), 8.25-  
8.30 (2H, m), 8.50 (1H, br s).

MS (FAB) m/z: 496 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 498 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>22</sub>N<sub>5</sub>O<sub>3</sub>ClS·HCl

5 Calculated: C, 54.14; H, 4.35; N, 13.15; Cl, 13.32; S,  
6.02.

Found: C, 53.94; H, 4.39; N, 12.82; Cl, 13.27; S,  
6.07.

[Example A-12] 4-[4-[[4-[(6-Chloronaphthalen-2-  
10 yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-  
methylpyridinium iodide

In a mixed solvent of benzene (10 ml) and methanol (10  
ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-  
yl)benzoyl]piperazine (300 mg) obtained in Example A-1 was  
15 dissolved at room temperature, followed by the addition of  
methyl iodide (1 ml). To the resulting mixture, the same  
amount of methyl iodide was added three times at intervals  
of 24 hours, followed by heating under reflux for 4 days.  
The reaction mixture was distilled under reduced pressure  
20 and the residue was washed with methanol, collected by  
filtration and dried, whereby the title compound (229 mg,  
58%) was obtained as a yellow solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.03 (2H, br s), 3.13 (2H, br s),  
3.43 (2H, br s), 3.75 (2H, br s), 4.34 (3H, s),  
25 7.59 (2H, d, J=8.8 Hz), 7.74 (1H, dd, J=8.8, 2.4 Hz),  
7.85 (1H, dd, J=8.8, 2.0 Hz), 8.08 (2H, d, J=8.8 Hz),

8.19 (1H, d, J=8.8Hz), 8.25-8.30 (2H, m), 8.45-8.55 (3H, m),  
9.03 (2H, d, J=6.8Hz).

Elementary analysis for  $C_{27}H_{25}N_3O_3ClIS \cdot H_2O$

Calculated: C, 49.74; H, 4.17; N, 6.45.

5 Found: C, 49.60; H, 4.09; N, 6.23.

[Example A-13] 3-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was  
conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-  
10 (pyridin-3-yl)benzoyl]piperazine, which had been obtained  
in Example A-5, as a starting material, whereby the title  
compound was obtained.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.90-3.40 (4H, m), 3.40-4.20 (4H, m), 7.50-  
7.60 (1H, m), 7.40-7.45 (3H, m), 7.54 (2H, d, J=8.3Hz),  
15 7.60 (1H, dd, J=8.8, 2.0Hz), 7.76 (1H, dd, J=8.8, 2.0Hz), 7.90-  
8.00 (3H, m), 8.22 (1H, d, J=5.9Hz), 8.31 (1H, d, J=2.0Hz),  
8.43 (1H, br s).

MS (FAB) m/z: 508  $[(M+H)^+, Cl^{35}]$ , 510  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{26}H_{22}N_3O_4ClS \cdot H_2O$

20 Calculated: C, 59.37; H, 4.60; N, 7.99; Cl, 6.74; S, 6.10.

Found: C, 59.48; H, 4.69; N, 7.74; Cl, 6.73; S, 6.07.

[Example A-14] 1-[2-Carboxy-4-(pyridin-4-yl)benzoyl]-4-  
[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (50 ml), 1-[2-tert-butoxycarbonyl-  
25 4-(pyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (250 g) was dissolved,

followed by the dropwise addition of trifluoroacetic acid (50 ml) under ice cooling. After stirring at room temperature for 5 hours, the solvent was distilled off. The residue was dissolved in methanol and the resulting solution was allowed to stand in a refrigerator for one day. The colorless solid so precipitated was collected by filtration and dried, whereby the title compound (550 mg, 28%) was obtained as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-3.40 (6H, m), 3.65-3.75 (2H, m), 7.41 (1H, d, J=7.8 Hz), 7.70-7.75 (3H, m), 7.82 (1H, dd, J=8.8, 2.0 Hz), 8.00 (1H, dd, J=7.8, 1.5 Hz), 8.15-8.30 (4H, m), 8.50 (1H, br s), 8.67 (2H, d, J=5.9 Hz), 13.29 (1H, br s).

MS (FAB) m/z: 536 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 538 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>27</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>5</sub>S·0.5H<sub>2</sub>O

Calculated: C, 59.50; H, 4.25; N, 7.71; Cl, 6.50; S, 5.88.

Found: C, 59.54; H, 4.30; N, 7.37; Cl, 6.35; S, 5.89.

[Example A-15] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)thiophen-2-yl]carbonyl]piperazine

hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 5-(pyridin-4-yl)thiophene-2-carboxylic acid hydrochloride obtained in Referential Example 28 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.11(4H, br s), 3.74(4H, br s),  
 7.52(1H, d,  $J=3.9\text{Hz}$ ), 7.73(1H, dd,  $J=8.8, 2.5\text{Hz}$ ),  
 7.83(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.03(1H, d,  $J=3.9\text{Hz}$ ), 8.10-  
 8.15(2H, m), 8.18(1H, d,  $J=8.8\text{Hz}$ ), 8.25-8.30(2H, m),  
 5 8.51(1H, s), 8.88(2H, d,  $J=6.8\text{Hz}$ ).

MS (FAB)  $m/z$ : 498  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 500  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_3\text{S}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$

Calculated: C, 52.17; H, 4.20; N, 7.61; Cl, 12.83; S,  
 11.61.

10 Found: C, 52.04; H, 4.22; N, 7.22; Cl, 12.74; S,  
 11.57.

[Example A-16] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
 [[5-(pyridin-4-yl)furan-2-yl]carbonyl]piperazine  
 hydrochloride

15 In the same manner as in Example A-4, a reaction was  
 conducted using 5-(pyridin-4-yl)furan-2-carboxylic acid  
 hydrochloride obtained in Referential Example 29 and 1-[(6-  
 chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as  
 starting materials, whereby the title compound was  
 20 obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.13(4H, br s), 3.30-4.00(4H, m),  
 7.21(1H, d,  $J=3.9\text{Hz}$ ), 7.71(1H, d,  $J=8.8\text{Hz}$ ), 7.75-7.80(1H, m),  
 7.83(1H, d,  $J=8.8\text{Hz}$ ), 8.10-8.30(5H, m), 8.51(1H, s), 8.85-  
 8.90(2H, m).

25 MS (FAB)  $m/z$ : 482  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 484  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot H_2O$

Calculated: C, 53.74; H, 4.32; N, 7.83; Cl, 13.22; S, 5.98.

Found: C, 53.51; H, 4.36; N, 7.57; Cl, 13.21; S, 5.97.

[Example A-17] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 4-(pyridin-2-yl)benzoic acid hydrochloride obtained in Referential Example 30 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.07(4H,br), 3.60-4.00(4H,br), 7.46(3H,br), 7.73(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,2.0Hz), 7.94-8.05(2H,br), 8.08(2H,d,J=8.8Hz), 8.18(1H,d,J=8.8Hz), 8.28(2H,d,J=8.8Hz), 8.50(1H,s), 8.70(1H,br).

MS (FAB) m/z: 492 [(M+H) $^+$ , Cl $^{35}$ ], 494 [(M+H) $^+$ , Cl $^{37}$ ].

Elementary analysis for  $C_{26}H_{22}ClN_3O_3S \cdot 0.9HCl \cdot H_2O$

Calculated: C, 57.53; H, 4.62; Cl, 12.41; N, 7.74; S, 5.91.

Found: C, 57.55; H, 4.52; Cl, 12.64; N, 7.61; S, 6.03.

[Example A-18] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-17, a reaction was conducted using 4-(2-pyridyl)benzoic acid hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as

starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.19(4H,br), 3.46(2H,br), 3.75(2H,br),  
7.36(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz), 7.50-7.58(1H,br),  
5 7.53(2H,d,J=7.8Hz), 7.57(2H,d,J=7.8Hz), 7.82(2H,d,J=7.8Hz),  
8.13(2H,m), 8.15(2H,d,J=7.8Hz), 8.75(1H,d,J=4.9Hz).

MS (FAB) m/z: 468 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 470 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·0.3EtOH·0.3H<sub>2</sub>O

Calculated: C, 56.42 H, 4.89; Cl, 13.54; N, 8.02; S, 6.12.

10 Found: C, 56.51 H, 4.83; Cl, 13.46; N, 8.10; S, 5.99.

[Example A-19] 2-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine, which had been obtained  
15 in Example A-17, as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.11(4H,br), 3.63(2H,br), 3.87(2H,br),  
7.27(1H,m), 7.33(1H,t,J=8.8Hz), 7.39-7.41(1H,br),  
20 7.40(2H,d,J=7.8Hz), 7.60(1H,d,J=8.8Hz), 7.77(1H,d,J=8.8Hz),  
7.83(2H,d,J=7.8Hz), 7.93(1H,d,J=3.8Hz), 7.94(1H,s),  
8.31(1H,s), 8.33(1H,d,J=5.9Hz).

MS (FAB) m/z: 508 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 510 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>4</sub>S

25 Calculated: C, 61.47; H, 4.37; Cl, 6.98; N, 8.27; S, 6.31.

Found: C, 61.32; H, 4.46; Cl, 7.21; N, 8.13; S, 6.02.

[Example A-20] 2-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

5 In the same manner as in Example A-12, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine, which had been obtained in Example A-17, as a starting material, whereby the title compound was obtained.

10  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.93-3.23(4H,br), 3.54(2H,br), 3.82(2H,br), 4.30(3H,s), 7.50(2H,d,J=8.8Hz), 7.53(1H,m), 7.70(2H,d,J=8.8Hz), 7.70(1H,br), 7.84-7.92(4H,m), 8.15(1H,t,J=6.8Hz), 8.26(1H,s), 8.52(1H,t,J=6.8Hz), 9.29(1H,d,J=5.9Hz).

15 Elementary analysis for  $\text{C}_{27}\text{H}_{25}\text{ClIN}_3\text{O}_3\text{S}\cdot 1.6\text{H}_2\text{O}$

Calculated: C, 48.93; H, 4.29; N, 6.34.

Found: C, 48.81; H, 4.06; N, 6.31.

[Example A-21] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2,4-diaminopyrimidin-6-yl)benzoyl]piperazine hydrochloride

20 In the same manner as in Example A-4, a reaction was conducted using 4-(2,4-diamino-6-pyrimidyl)benzoic acid hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

25  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.14(4H,br), 3.45(2H,br s), 3.73(2H,br s), 6.36(1H,s), 7.54(2H,d,J=7.8Hz),

7.74 (1H, dd, J=8.8, 2.0Hz), 7.82 (1H, d, J=8.8Hz), 7.83 (1H, s),  
 7.84 (2H, d, J=7.8Hz), 8.18 (1H, J=8.8Hz), 8.18-8.35 (3H, br),  
 8.27 (1H, s), 8.28 (1H, d, J=8.8Hz), 8.50 (1H, s), 12.64 (1H, br s).  
 MS (FAB) m/z: 523 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 525 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 Elementary analysis for C<sub>25</sub>H<sub>23</sub>ClN<sub>6</sub>O<sub>3</sub>S·HCl·1.4H<sub>2</sub>O

Calculated: C, 51.36; H, 4.62; Cl, 12.13; N, 14.37; S,  
 5.48.

Found: C, 51.38; H, 4.54; Cl, 12.24; N, 14.23; S,  
 5.55.

10 [Example A-22] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(2,4-  
 diaminopyrimidin-6-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-21, a reaction was  
 conducted using 4-(2,4-diamino-6-pyrimidyl)benzoic acid  
 hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl]piperazine  
 15 hydrochloride obtained in Referential Example 31 as  
 starting materials, whereby the title compound was  
 obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.18 (4H, br), 3.43 (2H, br), 3.76 (2H, br),  
 4.0 (2H, br), 6.37 (1H, s), 7.84 (2H, d, J=15.6Hz),  
 20 7.44 (1H, J=15.6Hz), 7.53 (2H, d, J=8.8Hz), 7.63 (2H, d, J=8.8Hz),  
 7.82 (1H, d, J=8.8Hz), 7.88 (1H, d, J=8.8Hz), 8.23 (1H, br s),  
 8.32 (1H, br s), 12.58 (1H, br s).

MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>23</sub>H<sub>23</sub>ClN<sub>6</sub>O<sub>3</sub>S·1.2HCl·1.4H<sub>2</sub>O

25 Calculated: C, 48.64; H, 4.79; Cl, 13.73; N, 14.80; S,  
 5.65.



Found: C, 48.46; H, 4.56; Cl, 13.53; N, 14.54; S, 5.72.

[Example A-23] 2-[4-[[4-[(E)-4-Chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-1, a reaction was conducted using 2-[4-[(1-piperazyl)carbonyl]phenyl]pyridine N-oxide hydrochloride and (E)-4-chlorostyrylsulfonyl chloride (WO/96/10022) as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.10-3.40 (4H, br), 3.66 (2H, br), 3.89 (2H, br), 6.65 (1H, d, J=15.6 Hz), 7.28 (1H, m), 7.34 (1H, t, J=7.8 Hz), 7.39-7.48 (6H, m), 7.50 (2H, d, J=7.8 Hz), 7.88 (2H, d, J=7.8 Hz), 8.34 (1H, d, J=5.9 Hz).

MS (FD) m/z: 483 (M<sup>+</sup>, Cl<sup>35</sup>), 485 (M<sup>+</sup>, Cl<sup>37</sup>).

Elementary analysis for C<sub>24</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>4</sub>S·0.5H<sub>2</sub>O

Calculated: C, 58.47; H, 4.70; Cl, 7.19; N, 8.52; S, 6.50.

Found: C, 58.49; H, 4.80; Cl, 7.29; N, 8.31; S, 6.34.

[Example A-24] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

Under ice cooling, piperazine (727 mg) was dissolved in dichloromethane (10 ml), followed by the addition of (E)-4-chlorostyrylsulfonyl chloride (WO96/10022) (500 mg) in portions. After stirring at room temperature for one hour, the reaction mixture was diluted with dichloromethane (100 ml), washed with a saturated aqueous NaCl solution

solution of sodium bicarbonate, a 5% aqueous solution of citric acid, water and saturated saline and then dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was suspended in N,N-dimethylformamide (10 ml), followed by the addition of 4-(4-pyridyl)benzoic acid (420 mg) obtained in Referential Example 2 and N,N-dimethyl-4-aminopyridine (309 mg). Under ice cooling, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (405 mg) was added and the resulting mixture was stirred at room temperature for 68 hours. After concentration, the residue was purified by chromatography on a silica gel column (dichloromethane : methanol = 70:1). The colorless solid so obtained was recrystallized from a mixed solvent of ethyl acetate and hexane, followed by recrystallization from ethyl acetate to obtain colorless needle crystals (185 mg). To the filtrate, on the other hand, saturated hydrochloric acid - ethanol (4 ml) was added. After concentration, the residue was recrystallized from methanol - ethyl acetate, whereby the title compound (200 mg) was obtained as colorless needle crystals.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.17(2H, br s), 3.23(2H, br s), 3.48(2H, br s), 3.77(2H, br s), 7.36(1H, d,  $J=15.3\text{Hz}$ ), 7.44(1H, d,  $J=15.3\text{Hz}$ ), 7.53(2H, d,  $J=8.8\text{Hz}$ ), 7.64(2H, d,  $J=8.3\text{Hz}$ ), 7.82(2H, d,  $J=8.3\text{Hz}$ ), 8.06(2H, d,  $J=8.8\text{Hz}$ ), 8.32(2H, d,  $J=6.6\text{Hz}$ ), 8.95(2H, d,  $J=6.6\text{Hz}$ ).

MS (FAB) m/z: 468 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 470 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for

C<sub>24</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·0.2H<sub>2</sub>O·0.22CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>

Calculated: C, 56.66; H, 4.81; Cl, 13.44; N, 7.97; S, 6.08.

5 Found: C, 56.68; H, 4.79; Cl, 13.43; N, 8.04; S, 6.14.

[Example A-25] 4-[4-[[4-[(E)-4-chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

10 In the same manner as in Example A-12, a reaction was conducted using 1-[(E)-4-chlorostyrylsulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine, which had been obtained in Example A-24, as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.04-3.87(8H,br), 4.35(3H,s),  
15 7.35(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz),  
7.53(2H,d,J=8.3Hz), 7.67(2H,d,J=8.3Hz), 7.82(2H,d,J=8.8Hz),  
8.13(2H,d,J=8.3Hz), 8.53(2H,d,J=6.8Hz), 9.05(2H,d,J=7.3Hz).

Elementary analysis for C<sub>25</sub>H<sub>25</sub>ClIN<sub>3</sub>O<sub>3</sub>S·0.5H<sub>2</sub>O

Calculated: C, 48.52; H, 4.23; N, 6.79.

20 Found: C, 48.68; H, 4.13; N, 6.41.

[Example A-26] 3-[4-[[4-[(E)-4-chlorostyrylsulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25 After the protective group was removed by the reaction as in Example A-7, the reaction with (E)-4-chlorostyrylsulfonyl chloride (W096/10022) was effected in

the same manner as in Example A-23, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.26(4H,br), 3.52-4.00(4H,br),  
6.64(1H,d,J=15.6Hz), 7.45-7.52(7H,m), 7.52(2H,d,J=2.0Hz),  
5 7.57(2H,d,J=2.0Hz), 8.22(1H,dt,J=6.3,1.6Hz),  
8.44(1H,t,J=1.6Hz).

MS (FAB) m/z: 484 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 486 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S·0.5H<sub>2</sub>O

Calculated: C, 58.47; H, 4.70; Cl, 7.19; N, 8.52; S, 6.50.

10 Found: C, 58.49; H, 4.66; Cl, 7.40; N, 8.54; S, 6.56.

[Example A-27] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-17 except for the use, as starting materials, of 4-(3-pyridyl)benzoic acid  
15 hydrochloride and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride, a reaction was conducted, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.08-3.29(4H,br), 3.42-3.85(4H,br),  
7.35(1H,d,J=15.6Hz), 7.43(1H,d,J=15.6Hz),  
20 7.52(2H,d,J=8.3Hz), 7.59(2H,d,J=8.3Hz), 7.80-7.93(5H,m),  
8.54(1H,d,J=6.8Hz), 8.78(1H,d,J=4.5Hz), 9.13(1H,d,J=2.0Hz).

MS (FAB) m/z: 468 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 470 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·1.3H<sub>2</sub>O

Calculated: C, 54.61; H, 4.89; N, 7.96; Cl, 13.43; S, 6.07.

25 Found: C, 54.82; H, 4.80; N, 7.91; Cl, 13.14; S, 6.14.

[Example A-28] 3-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-1-methylpyridinium iodide

In the same manner as in Example A-12, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-3-yl)benzoyl]piperazine, which had been obtained in Example A-5, as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.50-3.80 (8H, m), 4.44 (3H, s), 7.57 (2H, d, J=8.3Hz), 7.74 (1H, dd, J=8.8, 2.0Hz), 7.84 (1H, dd, J=8.8, 1.5Hz), 7.94 (2H, d, J=8.3Hz), 8.10-8.30 (4H, m), 8.51 (1H, s), 8.90 (1H, d, J=7.8Hz), 9.01 (1H, d, J=5.9Hz), 9.45 (1H, s).

MS (FAB) m/z: 506 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 508 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-29] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[2-hydroxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 2-(hydroxy-4-(4-pyridyl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-3.40 (8H, m), 7.25-7.40 (3H, m), 7.70-7.80 (1H, m), 7.80-7.90 (1H, m), 8.15-8.25 (3H, m), 8.25-8.35 (2H, m), 8.50-8.60 (1H, m), 8.91 (2H, d, J=6.4Hz), 10.41 (1H, br s).

MS (FAB)  $m/z$ : 535  $[(M+H)^+, Cl^{35}]$ , 537  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{26}H_{22}ClN_3O_4S \cdot 1.1HCl \cdot 1.7H_2O$

Calculated: C, 53.96; H, 4.62; N, 7.26; Cl, 12.86; S, 5.54.

Found: C, 53.62; H, 4.58; N, 7.34; Cl, 13.10; S, 5.94.

5 [Example A-30] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-methoxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 3-methoxy-4-(4-pyridyl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was  
10 obtained.

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.00-4.00 (8H, m), 3.81 (3H, s),  
7.08 (1H, d,  $J=8.8$  Hz), 7.17 (1H, s), 7.55 (1H, d,  $J=8.8$  Hz),  
7.74 (1H, dd,  $J=8.8, 2.0$  Hz), 7.83 (1H, d,  $J=8.3$  Hz),  
15 8.04 (2H, d,  $J=6.3$  Hz), 8.19 (1H, d,  $J=8.8$  Hz), 8.25-8.30 (2H, m),  
8.52 (1H, s), 8.85 (2H, d,  $J=6.3$  Hz).

MS (FAB)  $m/z$ : 522  $[(M+H)^+, Cl^{35}]$ , 524  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{27}H_{24}ClN_3O_4S \cdot 0.8HCl \cdot 1.7H_2O$

Calculated: C, 55.74; H, 4.89; N, 7.22; Cl, 10.97; S, 5.51.

20 Found: C, 55.59; H, 4.90; N, 7.23; Cl, 10.90; S, 5.52.

[Example A-31] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-hydroxy-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In dichloromethane (1 ml), boron tribromide (115  $\mu$ l) was dissolved, followed by the dropwise addition of a  
25 solution of 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[3-methoxy-4-(pyridin-4-yl)benzoyl]piperazine, which had been

obtained in Example A-30, in dichloromethane  
(dichloromethane: 4 ml) at an external temperature of about  
-78°C. While heating gradually to room temperature, the  
resulting mixture was stirred for 23 hours. After  
5 dichloromethane and water were added to the reaction  
mixture and the resulting mixture was stirred for a while,  
sodium bicarbonate was added to make alkaline the reaction  
mixture, which was separated into an organic layer and a  
water layer. From the water layer, another organic layer  
10 was extracted with dichloromethane. These organic layers  
were combined together, washed with saturated aqueous NaCl  
solution and then dried over anhydrous sodium sulfate. The  
residue obtained by distilling off the solvent under  
reduced pressure was purified by chromatography on a silica  
15 gel column (dichloromethane ~ 3% methanol -  
dichloromethane). The crudely purified product so obtained  
was dissolved in tetrahydrofuran. Solution of  
hydrochloride in ethanol was added to the resulting  
solution to solidify the same. The resulting solid was  
20 collected by filtration and then dissolved in a mixed  
solvent of water and methanol. After the removal of the  
insoluble matter by filtration, the filtrate was distilled  
under reduced pressure, whereby the title compound (36 mg,  
30%) was obtained.

25  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.00-3.80(8H,m), 6.85-6.95(1H,m),  
7.01(1H,d,J=1.4Hz), 7.49(1H,d,J=8.8Hz),

7.72 (1H, dd, J=8.8, 2.0 Hz), 7.81 (1H, dd, J=8.5, 1.7 Hz),  
 7.94 (2H, d, J=6.4 Hz), 8.19 (1H, d, J=8.8 Hz), 8.25-8.30 (2H, m),  
 8.51 (1H, s), 8.75 (2H, d, J=5.9 Hz), 10.67 (1H, s).

MS (FAB) m/z: 508 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 510 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example A-32] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-7, a reaction was effected using 4-tert-butoxycarbonyl-1-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine  
 10 as a starting material and the protective group was removed. The residue was then reacted with 4-(4-pyridyl)benzoic acid hydrochloride as in Example A-4, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.80-1.10 (3H, m), 3.00-4.00 (8H, m), 4.60-  
 15 4.80 (1H, m), 7.42 (2H, d, J=7.8 Hz), 7.47 (2H, d, J=5.9 Hz), 7.50-7.60 (1H, m), 7.64 (2H, d, J=8.3 Hz), 7.70-7.80 (1H, m), 7.85-7.95 (3H, m), 8.33 (1H, s), 8.69 (2H, s).

MS (FAB) m/z: 564 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 566 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>29</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>5</sub>S·0.3H<sub>2</sub>O

20 Calculated: C, 60.78; H, 4.70; N, 7.33; Cl, 6.80; S, 5.60.  
 Found: C, 60.84; H, 4.84; N, 6.98; Cl, 7.03; S, 5.70.

[Example A-33] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine-2-carboxylic acid

In the same manner as in Example A-3, the title  
 25 compound was obtained using 1-[(6-chloronaphthalen-2-



yl)sulfonyl]-2-ethoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.70-5.00 (7H,m), 7.40-7.50 (2H,m), 7.65-7.75 (2H,m), 7.85-8.25 (8H,m), 8.50-8.60 (2H,m), 8.80-8.95 (2H,m).

MS (FAB) m/z: 536 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 538 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>27</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>5</sub>S·0.3HCl·H<sub>2</sub>O

Calculated: C, 57.40; H, 4.34; N, 7.44; Cl, 8.16; S, 5.68.

Found: C, 57.16; H, 4.35; N, 7.36; Cl, 7.92; S, 6.08.

[Example A-34] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-3-yl)benzoyl]piperazine

In the same manner as in Example A-2, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.15-1.30 (3H,m), 2.60-4.60 (8H,m), 5.33 (1H,br), 7.40-7.55 (3H,m), 7.70-7.85 (4H,m), 8.05-8.10 (1H,m), 8.19 (1H,d,J=8.8Hz), 8.25-8.30 (2H,m), 8.50-8.65 (2H,m), 8.91 (1H,s).

MS (FAB) m/z: 564 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 566 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>29</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>5</sub>S·0.1HCl·0.5H<sub>2</sub>O

Calculated: C, 60.40; H, 4.74; N, 7.29; Cl, 6.76; S, 5.56.

Found: C, 60.67; H, 4.61; N, 7.30; Cl, 6.89; S, 5.51.

[Example A-35] 2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-3-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-3, with 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-3-yl)benzoyl]piperazine (426 mg) as a starting material, a crude product was obtained by the hydrolysis of the ester, followed by suspension in N,N-dimethylformamide (35 ml). Under ice cooling, di-tert-butyl dicarbonate (646 mg), pyridine (370  $\mu$ l) and ammonium bicarbonate (196 mg) were added to the resulting suspension. The resulting mixture was stirred at room temperature for 19 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (4% methanol - dichloromethane) and the eluate was dissolved in tetrahydrofuran. Solution of hydrochloride in ethanol was added to the resulting solution to solidify the same. The resulting solid was collected by filtration and dissolved in a mixed solvent of water and methanol. The insoluble matter was filtered off and the filtrate was distilled under reduced pressure, whereby the title compound (302 mg, 65%) was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.30-4.50 (6H,m), 5.08 (1H,br), 7.40-7.60 (2H,m), 7.65-7.85 (3H,m), 7.92 (2H,d,J=7.8Hz), 8.00-8.10 (1H,m), 8.20 (2H,d,J=8.8Hz), 8.25-8.35 (2H,m), 8.49 (1H,s), 8.80 (1H,d,J=7.8Hz), 8.88 (1H,d,J=5.4Hz), 9.25 (1H,s).

MS (FAB)  $m/z$ : 535  $[(M+H)^+, Cl^{35}]$ , 537  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{27}H_{23}ClN_4O_4S \cdot 1.1HCl \cdot 1.7H_2O$

Calculated: C, 53.54; H, 4.58; N, 9.25; Cl, 12.29; S, 5.29.

Found: C, 53.36; H, 4.71; N, 9.07; Cl, 12.17; S, 5.50.

[Example A-36] 2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine  
5 hydrochloride

In the same manner as in Example A-35, the title compound was obtained using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]piperazine as a starting material.

10  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.30-2.70 (2H,m), 3.20-3.80 (2H,m), 4.10-4.50 (2H,m), 5.07 (1H,br s), 7.40-7.55 (2H,m), 7.60-7.65 (1H,m), 7.67 (1H,s), 7.72 (1H,dd,  $J=8.8, 2.4\text{Hz}$ ), 7.78 (1H,dd,  $J=8.8, 2.4\text{Hz}$ ), 8.04 (2H,d,  $J=8.8\text{Hz}$ ), 8.20 (1H,d,  $J=8.8\text{Hz}$ ), 8.25-8.35 (4H,m), 8.49 (1H,s),  
15 8.95 (2H,d,  $J=5.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 535  $[(M+H)^+, \text{Cl}^{35}]$ , 537  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{27}\text{H}_{23}\text{ClN}_4\text{O}_4\text{S}\cdot\text{HCl}\cdot 1.8\text{H}_2\text{O}$

Calculated: C, 53.70; H, 4.61; N, 9.28; Cl, 11.74; S, 5.31.

Found: C, 53.87; H, 4.40; N, 8.89; Cl, 11.81; S, 5.23.

20 [Example A-37] 4-[4-[[2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-pyridin-4-yl]benzoyl]piperazine as a  
25 starting material, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.30-4.50 (6H,m), 5.04 (1H,br), 7.30-7.90 (10H,m), 8.10-8.30 (5H,m), 8.48 (1H,s).

MS (FAB)  $m/z$ : 551  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 553  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{27}\text{H}_{23}\text{ClN}_4\text{O}_5\text{S}\cdot 0.8\text{H}_2\text{O}$

5 Calculated: C, 57.35; H, 4.39; N, 9.91; Cl, 6.27; S, 5.67.

Found: C, 57.64; H, 4.50; N, 9.48; Cl, 6.37; S, 5.71.

[Example A-38] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 In the same manner as in Example A-37, a reaction was conducted, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30-1.40 (3H,m), 2.30-4.70 (8H,m), 5.47 (1H,br s), 7.40-7.80 (8H,m), 7.92 (1H,s), 7.94 (2H,s), 8.26 (2H,d,  $J=6.8\text{Hz}$ ), 8.48 (1H,s).

15 MS (FAB)  $m/z$ : 580  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 582  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{29}\text{H}_{26}\text{ClN}_3\text{O}_6\text{S}\cdot 1.3\text{H}_2\text{O}$

Calculated: C, 57.72; H, 4.78; N, 6.96; Cl, 5.87; S, 5.31.

Found: C, 57.99; H, 4.75; N, 6.56; Cl, 5.98; S, 5.43.

20 [Example A-39] 4-[4-[[2-Carboxy-4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-3, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.30-4.50 (6H,m), 5.22 (1H,br s), 7.35-7.50 (2H,m), 7.70-7.90 (6H,m), 8.19 (1H,d,  $J=8.8\text{Hz}$ ), 8.25-8.30 (4H,m), 8.53 (1H,s), 13.42 (1H,br).

25

Elementary analysis for  $C_{27}H_{22}ClN_3O_6S \cdot 0.2HCl \cdot 1.7H_2O$

Calculated: C, 54.97; H, 4.37; N, 7.12; Cl, 7.21; S, 5.44.

Found: C, 55.07; H, 4.40; N, 6.82; Cl, 7.16; S, 5.47.

[Example A-40] 2-Carbamoyl-4-[(E)-4-chlorostyrylsulfonyl]-

5 1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride, and  
2-Carbamoyl-4-[[2-(4-chlorophenyl)-2-ethoxyethyl]sulfonyl]-  
1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-35, a reaction was  
conducted, whereby the title compounds were obtained.

10 2-Carbamoyl-4-[(E)-4-chlorostyrylsulfonyl]-1-[4-(pyridin-4-  
yl)benzoyl]piperazine hydrochloride

$^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 2.80-4.80 (6H, m), 5.32 (1H, br),

7.04 (1H, d,  $J=15.6$  Hz), 7.40-7.50 (3H, m), 7.60-7.80 (4H, m),

7.95-8.05 (2H, m), 8.20 (2H, br), 8.81 (2H, br).

15 MS (FAB)  $m/z$ : 511  $[(M+H)^+, Cl^{35}]$ , 513  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{25}H_{23}ClN_4O_4S \cdot 0.9HCl \cdot 1.8H_2O$

Calculated: C, 52.11; H, 4.81; N, 9.72; Cl, 11.69.

Found: C, 52.28; H, 4.83; N, 9.44; Cl, 11.51.

2-Carbamoyl-4-[[2-(4-chlorophenyl)-2-ethoxyethyl]sulfonyl]-

20 1-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

$^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 1.10-1.20 (3H, m), 2.95-4.70 (6H, m),

5.34 (1H, br), 7.38 (4H, s), 7.65-7.85 (2H, m), 8.05-8.15 (2H, m),

8.40-8.50 (2H, m), 8.91 (2H, d,  $J=5.9$  Hz).

MS (FAB)  $m/z$ : 557  $[(M+H)^+, Cl^{35}]$ , 559  $[(M+H)^+, Cl^{37}]$ .

25 Elementary analysis for  $C_{27}H_{29}ClN_4O_5S \cdot HCl \cdot 2.5H_2O$

Calculated: C, 50.78; H, 5.52; N, 8.77; Cl, 11.10; S, 5.02.

Found: C, 50.61; H, 5.38; N, 8.68; Cl, 11.27; S, 5.07.

[Example A-41] 1-[trans-4-(Aminomethyl)cyclohexylmethyl]-  
4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
5 hydrochloride

In the same manner as in Example A-7, a reaction was  
conducted, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.80-1.00(4H,m), 1.48(1H,m), 1.60-

1.90(5H,m), 2.60(2H,m), 2.90-3.10(4H,m), 3.14(2H,m),

10 3.52(2H,m), 3.77(2H,m), 7.75(1H,dd,J=8.8,2.0Hz),

7.85(1H,d,J=8.8Hz), 7.99(3H,br), 8.21(1H,d,J=8.8Hz), 8.30-

8.40(2H,m), 8.56(1H,s), 10.46(1H,br).

MS (FAB) m/z: 436 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 438 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>30</sub>ClN<sub>3</sub>O<sub>2</sub>S·2HCl·3/4H<sub>2</sub>O

15 Calculated: C, 50.58; H, 6.46; N, 8.04; Cl, 20.36; S, 6.14.

Found: C, 50.74; H, 6.48; N, 7.76; Cl, 20.09; S, 6.19.

[Example A-42] 1-[trans-4-  
(Aminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-  
yl)sulfonyl]piperazine hydrochloride

20 In the same manner as in Example A-7, the title  
compound was obtained using 1-[trans-4-(N-tert-  
butoxycarbonylaminoethyl)cyclohexylcarbonyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
material.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 0.90-1.00 (2H,m), 1.20-1.40 (2H,m),  
 1.48 (1H,m), 1.50-1.70 (2H,m), 1.70-1.90 (2H,m), 2.44 (1H,m),  
 2.59 (2H,m), 2.96 (4H,m), 3.55 (4H,m),  
 7.72 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.81 (1H,d,  $J=8.3\text{Hz}$ ), 7.90 (3H,br),  
 5 8.16 (1H,d,  $J=8.8\text{Hz}$ ), 8.20-8.30 (2H,m), 8.49 (1H,s).

MS (FAB)  $m/z$ : 450  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 452  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{22}\text{H}_{28}\text{ClN}_3\text{O}_3\text{S}\cdot 0.9\text{HCl}\cdot 1.5\text{H}_2\text{O}$

Calculated: C, 51.83; H, 6.31; N, 8.24; Cl, 13.21; S, 6.29.

Found: C, 51.63; H, 6.22; N, 7.97; Cl, 13.32; S, 6.17.

10 [Example A-43] 1-[N-[trans-4-(Aminomethyl)cyclohexylcarbonyl]glycyl]]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-7, a reaction was  
 conducted using 1-[N-[trans-4-(N-tert-  
 15 butoxycarbonylaminoethyl)cyclohexylcarbonyl]glycyl]]-4-  
 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
 material, whereby the title compound was obtained.

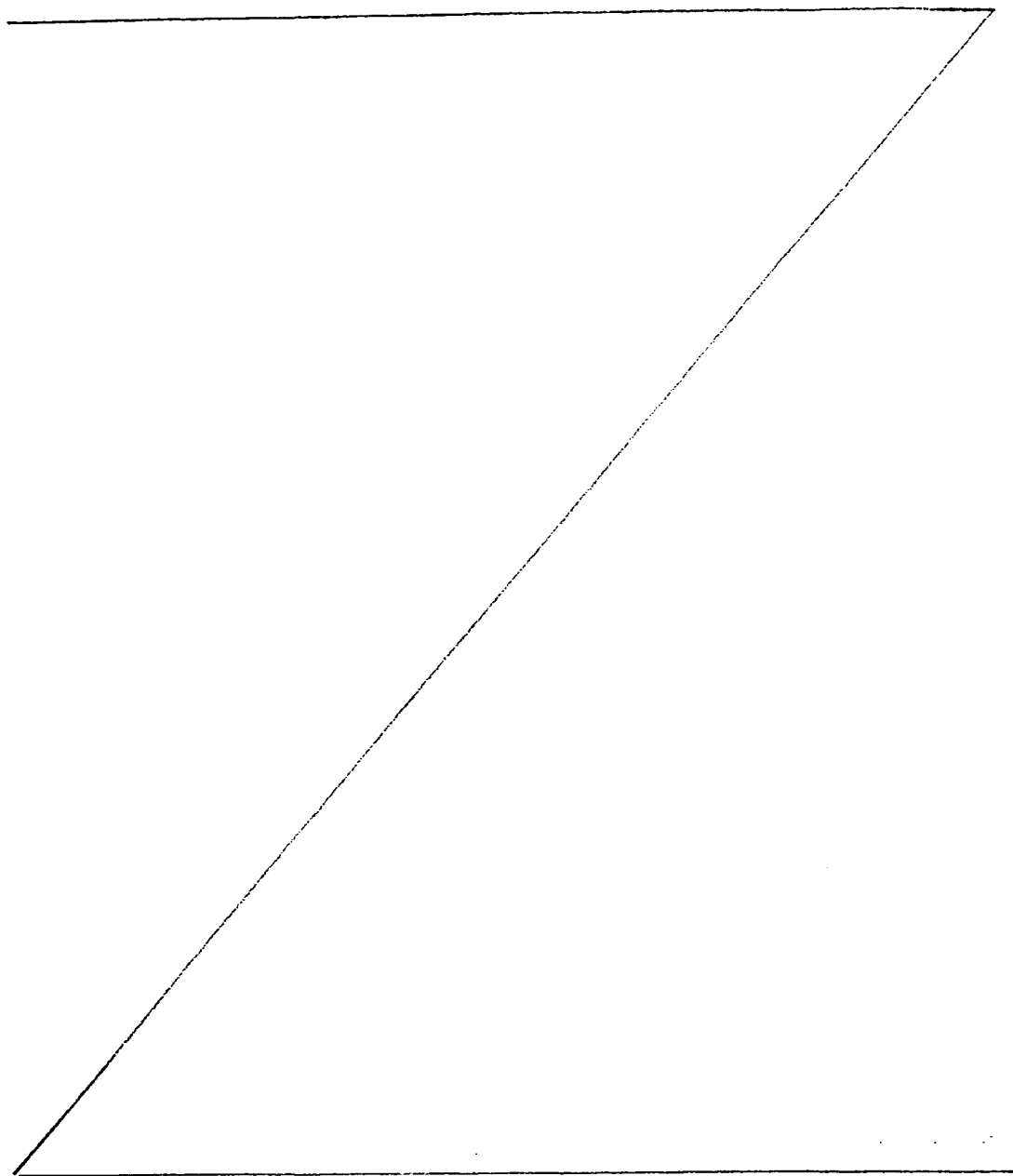
$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 0.80-1.00 (2H,m), 1.20-1.40 (2H,m),  
 1.50 (1H,m), 1.60-1.80 (4H,m), 2.10 (1H,m), 2.62 (2H,m), 2.90-  
 20 3.10 (4H,m), 3.40-3.60 (4H,m), 3.83 (2H,d,  $J=5.4\text{Hz}$ ), 7.70-  
 7.90 (3H,m), 7.93 (3H,br), 8.17 (1H,d,  $J=8.3\text{Hz}$ ), 8.20-  
 8.30 (2H,m), 8.49 (1H,s).

MS (FAB)  $m/z$ : 507  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 509  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{24}\text{H}_{31}\text{ClN}_4\text{O}_4\text{S}\cdot \text{HCl}$

Calculated: C, 53.04; H, 5.93; N, 10.31; Cl, 13.05; S,  
5.90.

Found: C, 52.90; H, 5.98; N, 10.29; Cl, 12.98; S,  
5.91.





[Example A-44] 1-[trans-4-(Aminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[trans-4-(N-tert-butoxycarbonylaminoethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine as a starting material.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 0.90-1.10 (2H,m), 1.30-1.50 (2H,m), 1.50-1.90 (7H,m), 2.40-2.80 (3H,m), 3.20-3.70 (8H,m), 7.60-7.70 (1H,m), 7.80-8.00 (4H,m), 8.10-8.20 (1H,m), 8.20-8.30 (2H,m), 8.52 and 8.53 (1H, each s).

MS (FAB)  $m/z$ : 464  $[(M+H)^+, \text{Cl}^{35}]$ , 466  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{23}\text{H}_{30}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}$

Calculated: C, 55.20; H, 6.24; N, 8.40; Cl, 14.17; S, 6.41.

Found: C, 55.42; H, 6.18; N, 8.26; Cl, 14.11; S, 6.53.

[Example A-45] 1-[4-(Aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-(N-tert-butoxycarbonylaminoethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.00-3.20 (4H,br), 3.30-3.80 (4H,br), 4.03 (2H,s), 7.37 (2H,d,J=7.3Hz), 7.50 (2H,d,J=7.3Hz), 7.72 (1H,d,J=8.8Hz), 7.82 (1H,d,J=8.8Hz), 8.18 (1H,d,J=8.8Hz),

8.20-8.40 (2H,m), 8.43 (3H,br), 8.49 (1H,s).

MS (FAB) m/z: 444 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 446 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·H<sub>2</sub>O

Calculated: C, 53.02; H, 5.06; N, 8.43; Cl, 14.23; S, 6.43.

5 Found: C, 53.06; H, 5.30; N, 8.32; Cl, 14.20; S, 6.44.

[Example A-46] 1-[3-(Aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-3, the ester was hydrolyzed using methyl 3-(N-tert-butoxycarbonylaminomethyl)benzoate as a starting material. Reaction was then effected as in Example A-4 or A-7, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.07 (4H,br), 3.20-3.80 (4H,br), 4.00 (2H,s), 7.30-7.60 (4H,m), 7.73 (1H,d,J=8.8Hz), 7.83 (1H,d,J=8.8Hz), 8.10-8.60 (7H,m).

MS (FAB) m/z: 444 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 446 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·1/4H<sub>2</sub>O

Calculated: C, 54.49; H, 4.88; N, 8.67; Cl, 14.62; S, 6.61.

Found: C, 54.64; H, 4.95; N, 8.52; Cl, 14.59; S, 6.70.

20 [Example 47] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-[N-(1-pyrrolin-2-yl)aminomethyl]benzoyl]piperazine hydrochloride

In dimethylformamide (2 ml), 2-methoxy-1-pyrroline (35 mg) was dissolved, followed by the addition of 1-[3-(aminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (0.10 g) and

triethylamine (44  $\mu$ l). The resulting mixture was stirred at room temperature for 3 days. After the reaction mixture was concentrated under reduced pressure, the concentrate was diluted with methanol, followed by the addition of 1N hydrochloric acid. The solvent was then distilled off under reduced pressure. The residue was purified by gel permeation chromatography ("Sephadex LH-20",  $\varnothing$  15 x 300 mm, methanol), followed by solidification in a mixed solvent of methanol and ether, whereby a colorless solid (0.11 g, 91%) was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.04 (2H, m), 2.81 (2H, t,  $J=7.8\text{Hz}$ ), 3.18 (4H, br), 3.20-3.80 (5H, m), 4.10 (1H, br), 4.51 (2H, d,  $J=5.9\text{Hz}$ ), 7.30-7.50 (4H, m), 7.72 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.82 (1H, d,  $J=8.8\text{Hz}$ ), 8.18 (1H, d,  $J=8.8\text{Hz}$ ), 8.20-8.30 (2H, m), 8.50 (1H, s), 10.01 (1H, t,  $J=5.9\text{Hz}$ ), 10.06 (1H, s).

MS (FAB)  $m/z$ : 511  $[(M+H)^+, \text{Cl}^{35}]$ , 513  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{26}\text{H}_{27}\text{ClN}_4\text{O}_3\text{S} \cdot \text{HCl} \cdot \text{CH}_3\text{OH} \cdot 4/5\text{H}_2\text{O}$

Calculated: C, 54.60; H, 5.70; N, 9.43; Cl, 11.94; S, 5.40.

Found: C, 54.84; H, 5.47; N, 9.13; Cl, 11.86; S, 5.48.

[Example A-48] 1-[4-(2-Aminoethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-(2-(tert-

butoxycarbonylamino)ethyl]benzoyl]-4-[(6-chloronaphthalen-

2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-3.20(8H,m), 3.40-3.90(4H,br),  
7.28(4H,s), 7.72(1H,dd,J=8.8,2.4Hz),  
7.81(1H,dd,J=8.8,2.0Hz), 8.02(3H,br), 8.17(1H,d,J=8.3Hz),  
8.20-8.30(2H,m), 8.49(1H,s).

MS (FAB) m/z: 458 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 460 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>23</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·1/2CH<sub>3</sub>OH·1/2H<sub>2</sub>O

Calculated: C, 54.34; H, 5.43; N, 8.09; Cl, 13.65; S, 6.17.

Found: C, 54.43; H, 5.26; N, 7.92; Cl, 13.58; S, 6.24.

[Example A-49] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-  
[[ (3S)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title  
compound was obtained using 1-[4-[[ (3S)-1-tert-  
butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.05-2.25(2H,m), 3.00-3.10(4H,m), 3.20-  
3.70(8H,m), 5.16(1H,br s), 6.95(2H,d,J=8.8Hz),  
7.31(2H,d,J=8.3Hz), 7.70-7.75(1H,m),  
7.82(1H,dd,J=8.5,1.7Hz), 8.18(2H,d,J=8.8Hz), 8.20-  
8.30(2H,m), 8.50(1H,s).

MS (FAB) m/z: 500 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 502[(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-50] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-  
[[ (3S)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example 7, the title compound

was obtained using 1-[3-[[[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.00-2.20 (2H,m), 2.95-3.15 (4H,m), 3.20-3.80 (8H,m), 5.11 (1H,br s), 6.90-6.95 (3H,m), 7.00-7.05 (1H,m), 7.30-7.35 (1H,m), 7.72 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.81 (1H,dd,  $J=8.5, 1.7\text{Hz}$ ), 8.18 (2H,d,  $J=8.8\text{Hz}$ ), 8.25-8.30 (2H,m), 8.50 (1H,s).

10 MS (FAB)  $m/z$ : 500  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 502  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{25}\text{H}_{26}\text{ClN}_3\text{O}_4\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}$

Calculated: C, 54.15; H, 5.27; N, 7.58; Cl, 12.79; S, 5.78.

Found: C, 53.84; H, 5.19; N, 7.33; Cl, 12.72; S, 5.86.

[Example A-51] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-  
15 [[(3R)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-[[[(3R)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
20 material.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.05-2.25 (2H,m), 3.00-3.10 (4H,m), 3.20-3.70 (8H,m), 5.16 (1H,br s), 6.96 (2H,d,  $J=8.8\text{Hz}$ ), 7.31 (2H,d,  $J=8.8\text{Hz}$ ), 7.74 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.82 (1H,dd,  $J=8.8, 1.5\text{Hz}$ ), 8.18 (1H,d,  $J=8.8\text{Hz}$ ), 8.25-  
25 8.30 (2H,m), 8.50 (1H,s).

MS (FAB) m/z: 500 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 502 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>4</sub>S·1.2HCl·0.8H<sub>2</sub>O

Calculated: C, 53.80; H, 5.20; N, 7.53; Cl, 13.97; S, 5.74.

5 Found: C, 53.84; H, 5.05; N, 7.51; Cl, 13.79; S, 5.74.

[Example A-52] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-  
[[ (3R)-pyrrolidin-3-yl]oxy]benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title  
compound was obtained using 1-[3-[[ (3R)-1-tert-  
10 butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.00-2.20 (2H, m), 2.95-3.15 (4H, m), 3.20-  
3.80 (8H, m), 5.11 (1H, br s), 6.90-6.95 (2H, m), 7.00-  
15 7.05 (1H, m), 7.30-7.35 (1H, m), 7.74 (1H, dd, J=8.8, 2.0 Hz),  
7.82 (1H, dd, J=8.8, 1.5 Hz), 8.18 (2H, d, J=8.8 Hz), 8.25-  
8.30 (2H, m), 8.50 (1H, s).

MS (FAB) m/z: 500 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 502 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>4</sub>S·HCl·H<sub>2</sub>O

20 Calculated: C, 54.15; H, 5.27; N, 7.58; Cl, 12.79; S, 5.78.

Found: C, 53.91; H, 5.14; N, 7.37; Cl, 12.62; S, 5.67.

[Example A-53] 1-[4-(2-Aminopyrimidin-5-yl)benzoyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was  
25 conducted using 4-(2-amino-5-pyrimidyl)benzoic acid and 1-  
[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.06(4H,br), 3.56 and (each 2H,br),  
4.70-5.45(3H,br), 7.40(2H,d,J=8.8Hz), 7.67(2H,d,J=8.8Hz),  
5 7.73(1H,dd,J=8.8,2.0Hz), 7.82(1H,d,J=8.8Hz),  
8.18(1H,d,J=8.8Hz), 8.27(1H,s), 8.28(1H,d,J=8.8Hz),  
8.50(1H,s), 8.72(1H,s).

MS (FAB) m/z: 508 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 510 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>3</sub>S·1.1HCl·0.7H<sub>2</sub>O

10 Calculated: C, 53.55; H, 4.40; Cl, 13.28; N, 12.49; S,  
5.72.

Found: C, 53.59; H, 4.58; Cl, 13.02; N, 12.58; S,  
5.89.

[Example A-54] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
15 [(piperidin-4-yl)acetyl]piperazine hydrochloride

In the same manner as in Example A-7, the title  
compound was obtained using 1-[(1-tert-  
butoxycarbonylpiperidin-4-yl)acetyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
20 material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.25(2H,m), 1.71(2H,m), 1.87(1H,m),  
2.20(2H,d,J=6.8Hz), 2.78(2H,br), 2.96(4H,br s), 3.14(2H,m),  
3.52(4H,br s), 4.02(2H,br), 7.73(1H,dd,J=8.8,2.0Hz),  
7.81(1H,d,J=8.8Hz), 8.17(1H,d,J=8.8Hz), 8.28(1H,d,J=8.8Hz),  
25 8.26(1H,s), 8.50(1H,s), 8.54(1H,br), 8.75(1H,br).

MS (FAB) m/z: 436 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 438 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>21</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>3</sub>S·1.1HCl·1.1H<sub>2</sub>O

Calculated: C, 50.86; H, 5.96; Cl, 15.01; N, 8.47; S, 6.47.

Found: C, 51.07; H, 5.74; Cl, 14.75; N, 8.36; S, 6.50.

5 [Example A-55] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(piperidin-4-yl)propionyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[3-(1-tert-butoxycarbonylpiperidin-4-yl)propionyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)δ: 1.29(2H,m), 1.50(1H,m), 1.51(2H,m), 1.89(2H,m), 2.36(2H,m), 2.88(2H,m), 3.08(4H,m), 3.64(4H,m), 4.04(2H,br), 7.58(1H,dd,J=8.8,2.0Hz), 7.82(1H,dd,J=8.8,2.0Hz), 8.05(1H,d,J=8.8Hz), 8.06(1H,s), 8.09(1H,d,J=8.8Hz), 8.42(1H,s).

MS (FAB) m/z: 450 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 452 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>3</sub>S·1.8HCl·0.9H<sub>2</sub>O

Calculated: C, 49.68; H, 5.99; Cl, 18.66; N, 7.90; S, 6.03.

20 Found: C, 49.45; H, 5.70; Cl, 18.63; N, 7.72; S, 6.04.

[Example A-56] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(E)-3-(pyridin-3-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example A-4, the title compound was obtained using (E)-3-(3-pyridyl)acrylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.



$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.03 (4H, m), 3.69 (2H, br), 3.85 (2H, br),  
 7.51 (2H, s), 7.70 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
 7.83 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.89 (1H, dd,  $J=7.8, 5.4\text{Hz}$ ),  
 8.16 (1H, d,  $J=8.8\text{Hz}$ ), 8.22 (1H, d,  $J=2.0\text{Hz}$ ), 8.26 (1H, d,  $J=8.8\text{Hz}$ ),  
 5 8.51 (1H, s), 8.67 (1H, d,  $J=7.8\text{Hz}$ ), 8.77 (1H, d,  $J=5.4\text{Hz}$ ),  
 9.13 (1H, s).

MS (FAB)  $m/z$ : 442  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 444  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{22}\text{H}_{20}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot 1/4\text{H}_2\text{O}$

Calculated: C, 54.72; H, 4.49; N, 8.70; Cl, 14.68; S, 6.64.

10 Found: C, 54.81; H, 4.43; N, 8.54; Cl, 14.68; S, 6.74.

[Example A-57] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
 [(E)-3-(pyridin-4-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example A-4, the title  
 compound was obtained using (E)-3-(4-pyridyl)acrylic acid  
 15 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
 hydrochloride as starting materials.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.03 (4H, m), 3.68 (2H, br), 3.82 (2H, br),  
 5.76 (1H, s), 7.48 (1H, d,  $J=15.1\text{Hz}$ ), 7.65 (1H, d,  $J=15.1\text{Hz}$ ),  
 7.72 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.83 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
 20 8.11 (2H, br s), 8.16 (1H, d,  $J=8.8\text{Hz}$ ), 8.24 (1H, s),  
 8.27 (1H, d,  $J=8.8\text{Hz}$ ), 8.52 (1H, s), 8.82 (2H, d,  $J=5.9\text{Hz}$ ).

MS (FAB)  $m/z$ : 442  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 444  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{22}\text{H}_{20}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot 1/5\text{H}_2\text{O}$

Calculated: C, 54.82; H, 4.48; Cl, 14.71; N, 8.72; S, 6.65.

25 Found: C, 54.77; H, 4.41; Cl, 14.71; N, 8.50; S, 6.77.

[Example A-58] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(pyridin-4-yl)acetyl]piperazine hydrochloride

In the same manner as in Example A-4, the title compound was obtained using 4-pyridylacetic acid

5 hydrochloride and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.99(2H,br), 3.04(2H,br), 3.57(2H,br),  
3.62(2H,br), 4.00(2H,s), 7.71(2H,d,J=5.9Hz),  
7.74(1H,dd,J=8.8,3.0Hz), 7.83(1H,dd,J=8.8,2.0Hz),  
10 8.18(1H,d,J=8.8Hz), 8.27(1H,s), 8.29(1H,d,J=8.8Hz),  
8.53(1H,s), 8.72(2H,d,J=5.9Hz).

MS (FAB) m/z: 430 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 432 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>21</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·0.3H<sub>2</sub>O

Calculated: C, 53.46; H, 4.61; Cl, 15.03; N, 8.91; S, 6.80.

15 Found: C, 53.28; H, 4.49; Cl, 15.18; N, 8.91; S, 6.75.

[Example A-59] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[(3RS)-pyrrolidin-3-yl]benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-[(3RS)-1-tert-butoxycarbonylpyrrolidin-3-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.85-1.95(1H,m), 2.30-2.40(1H,m), 3.00-  
3.90(13H,m), 7.72(1H,dd,J=8.6,2.2Hz),

25 7.80(1H,dd,J=8.8,2.0Hz), 7.29(2H,d,J=8.3Hz),

7.35 (2H, d, J=8.3Hz), 8.18 (1H, d, J=8.8Hz), 8.25-8.30 (2H, m),  
8.49 (1H, s).

MS (FAB) m/z: 484 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 486 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·3/2H<sub>2</sub>O

5 Calculated: C, 54.84; H, 5.52; N, 7.67; Cl, 12.95; S, 5.86.

Found: C, 55.00; H, 5.53; N, 7.48; Cl, 13.23; S, 5.97.

[Example A-60] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[[ (1RS)-4-(pyridin-4-yl)-3-cyclohexene]carbonyl]piperazine  
hydrochloride

10 In the same manner as in Example A-4, a reaction was  
conducted using (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylic  
acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
hydrochloride as starting materials, whereby the title  
compound was obtained.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.50-1.60 (1H, m), 1.80-1.90 (1H, m), 2.25-  
2.58 (5H, m), 2.80-2.90 (1H, m), 2.91-3.10 (1H, m), 3.46-  
3.72 (4H, m), 6.94 (1H, br s), 7.71 (1H, dd, J=8.8, 2.0Hz),  
7.82 (1H, dd, J=8.8, 2.0Hz), 7.96 (2H, d, J=6.8Hz),  
8.15 (1H, J=8.8Hz), 8.24 (1H, J=2.0Hz), 8.27 (1H, J=8.8Hz),  
20 8.50 (1H, s), 8.76 (2H, d, J=6.8Hz).

MS (FAB) m/z: 496 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 498 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·1.3H<sub>2</sub>O

Calculated: C, 56.18; H, 5.37; Cl, 12.75; N, 7.56; S, 5.77.

Found: C, 56.03; H, 5.29; Cl, 12.67; N, 7.41; S, 5.77.

25 [Example A-61] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[[ (1RS)-4-  
(pyridin-4-yl)-3-cyclohexene]carbonyl]piperazine

hydrochloride

In the same manner as in Example A-4, a reaction was conducted using (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylic acid and 1-[(E)-4-chlorostyrylsulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.59-1.70(1H,m), 1.90-1.98(1H,m), 2.31-2.56(4H,m), 2.90-3.00(1H,m), 3.13(4H,br s), 3.50-3.63(4H,m), 6.98(1H,br s), 7.35(1H,d,J=15.6Hz), 7.44(1H,d,J=15.6Hz), 7.51(2H,d,J=8.3Hz), 7.80(1H,J=8.3Hz), 7.97(1H,J=6.8Hz), 8.77(1H,J=6.8Hz).

MS (FAB) m/z: 472 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 474 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>3</sub>S·0.9HCl·2.3H<sub>2</sub>O

Calculated: C, 52.77; H, 5.81; Cl, 12.33; N, 7.69; S, 5.87.

Found: C, 52.61; H, 5.80; Cl, 12.54; N, 7.44; S, 6.05.

[Example A-62] cis, trans-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[4-(pyridin-4-yl)cyclohexane]carbonyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using cis, trans-4-(4-pyridyl)cyclohexanecarboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

MS (FAB) m/z: 498 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 500 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>3</sub>S·1.3HCl·2H<sub>2</sub>O

Calculated: C, 53.71; H, 5.77; Cl, 14.02; N, 7.23; S, 5.51.

Found: C, 53.70; H, 5.70; Cl, 14.21; N, 7.13; S, 5.72.

[Example A-63] cis, trans-1-[(E)-4-Chlorostyrylsulfonyl]-  
4-[[4-(pyridin-4-yl)cyclohexane]carbonyl]piperazine  
5 hydrochloride

In the same manner as in Example A-4, a reaction was  
conducted using cis, trans-4-(4-  
pyridyl)cyclohexanecarboxylic acid and 1-[(E)-4-  
chlorostyrylsulfonyl]piperazine hydrochloride as starting  
10 materials, whereby the title compound was obtained.

MS (FAB) m/z: 474 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 476 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>3</sub>S·1.2HCl·0.8H<sub>2</sub>O

Calculated: C, 54.17; H, 5.83; Cl, 14.66; N, 7.80; S, 6.03.

Found: C, 54.21; H, 6.20; Cl, 15.03; N, 7.51; S, 6.18.

15 [Example A-64] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-  
(1,2,3,6-tetrahydropyridin-4-yl)benzoyl]piperazine  
hydrochloride

In the same manner as in Example A-7, the title  
compound was obtained using 1-4-(1-tert-butoxycarbonyl-  
20 1,2,3,6-tetrahydropyridin-4-yl)benzoyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.67(2H, br s), 3.05(4H, br), 3.30(2H, br  
s), 3.35-3.78(6H, m), 6.24(1H, br s), 7.32(2H, d, J=8.3Hz),  
25 7.47(2H, d, J=8.3Hz), 7.71(1H, dd, J=8.8, 2.0Hz),  
7.81(1H, dd, J=8.8, 2.0Hz), 8.17(1H, d, J=8.8Hz), 8.22-

8.28 (2H, m), 8.49 (1H, s), 9.25 (2H, br s).

MS (FAB) m/z: 496 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 498 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·2/5H<sub>2</sub>O

Calculated: C, 57.86; H, 5.19; Cl, 13.14; N, 7.79; S, 5.94.

5 Found: C, 57.91; H, 5.19; Cl, 12.91; N, 7.75; S, 5.78.

[Example A-65] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(piperidin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-7, the title compound was obtained using 1-[4-(1-tert-  
10 butoxycarbonylpiperidin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.78-1.94 (4H, m), 2.80-3.21 (7H, m), 3.30-  
3.84 (6H, m), 7.23 (2H, d, J=8.3 Hz), 7.28 (2H, d, J=8.3 Hz),  
15 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.80 (1H, dd, J=8.8, 2.0 Hz),  
8.17 (1H, d, J=8.8 Hz), 8.22-8.27 (2H, m), 8.49 (1H, s), 8.78-  
9.00 (2H, m).

MS (FAB) m/z: 498 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 500 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·3/5H<sub>2</sub>O

20 Calculated: C, 57.27; H, 5.58; Cl, 13.00; N, 7.71; S, 5.88.

Found: C, 57.23; H, 5.52; Cl, 12.90; N, 7.60; S, 5.83.

[Example A-66] (3RS)-3-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-[4-(pyridin-4-yl)benzoyl]pyrrolidine hydrochloride

25 In saturated solution of hydrochloride in ethanol,  
(3RS)-1-tert-butoxycarbonyl-3-[(6-chloronaphthalen-2-

yl)sulfonamido]pyrrolidine was dissolved, followed by stirring at room temperature for 8 hours. The solvent was then distilled off under reduced pressure. In the same manner as in Example A-4, a reaction was conducted using the resulting residue and 4-(4-pyridyl)benzoic acid as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.70-2.10 (2H,m), 3.00-3.65 (4H,m), 3.75-3.90 (1H,m), 7.50-8.40 (13H,m), 8.95-9.05 (2H,m).

MS (FAB)  $m/z$ : 492  $[(M+H)^+, \text{Cl}^{35}]$ , 494  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{26}\text{H}_{22}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot 1.8\text{H}_2\text{O}$

Calculated: C, 55.68; H, 4.78; N, 7.49; Cl, 12.64; S, 5.72.

Found: C, 55.62; H, 4.94; N, 7.67; Cl, 12.76; S, 5.79.

[Example A-67] (3RS)-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[4-(pyridin-4-yl)benzamido]pyrrolidine hydrochloride

In saturated solution of hydrochloride in ethanol, (3RS)-1-tert-butoxycarbonyl-3-[4-(4-pyridyl)benzamido]pyrrolidine was dissolved, followed by stirring at room temperature for 4 hours. The solvent was then distilled off under reduced pressure. In the same manner as in Example A-1, a reaction was conducted using the resulting residue and 6-chloro-2-naphthylsulfonyl chloride as starting materials, whereby the title compound was obtained as a hydrochloride.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.90-2.10 (2H,m), 3.00-3.60 (4H,m), 4.15-

4.25 (1H, m), 7.57 (1H, dd, J=8.8, 2.0 Hz), 7.73 (2H, d, J=8.8 Hz),  
 7.85 (1H, dd, J=8.8, 2.0 Hz), 7.90 (2H, d, J=8.8 Hz), 7.95-  
 8.05 (2H, m), 8.18 (1H, d, J=8.8 Hz), 8.30-8.40 (3H, m),  
 8.50 (1H, s), 8.98 (2H, d, J=6.4 Hz).

5 MS (FAB) m/z: 492 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 494 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S·0.8HCl·0.8H<sub>2</sub>O

Calculated: C, 58.31; H, 4.59; N, 7.85; Cl, 11.92; S, 5.99.

Found: C, 58.27; H, 4.68; N, 7.80; Cl, 11.94; S, 6.04.

[Example A-68] 1-[[ (E)-2-(6-Chloropyridin-3-

10 yl)ethylene]sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

To a suspension of 1-tert-butoxycarbonyl-4-[[ (E)-2-(6-chloropyridin-3-yl)ethylene]sulfonyl]piperazine (390 mg) in ethanol (2 ml), saturated hydrochloric acid - ethanol (6 ml) was added, followed by stirring for 3 hours. The  
 15 reaction mixture was concentrated and the residue was dissolved in N,N-dimethylformamide (10 ml). To the resulting solution, 4-(4-pyridyl)benzoic acid hydrochloride (262 mg) and N-methylmorpholine (1.00 ml) were added. Under ice cooling, 1H-benzotriazol-1-

20 yloxytripyrrolidinophosphonium hexafluorophosphate was

added, followed by stirring at room temperature for 4

hours. The reaction mixture was diluted with ethyl

acetate, washed successively with water, a saturated

aqueous solution of sodium bicarbonate and saturated

25 aqueous NaCl solution and then dried over anhydrous sodium

sulfate. The residue obtained by distilling off the



solvent under reduced pressure was recrystallized from a mixed solvent of dichloromethane and ethyl acetate. The resulting crystals were suspended in ethanol. Saturated hydrochloric acid - ethanol (6 ml) was added to the  
 5 resulting suspension, followed by concentration into its hydrochloride. The resulting solid was recrystallized from ethanol, whereby the title compound (245 mg, 47%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.10-3.31(4H,br), 3.40-3.84(4H,br),  
 10 7.50(1H,d,J=15.9Hz), 7.52(1H,d,J=15.9Hz),  
 7.46(3H,d,J=8.3Hz), 8.06(2H,d,J=8.3Hz), 8.28-8.33(3H,m),  
 8.79(1H,d,J=2.0Hz), 8.94(2H,d,J=6.4Hz).

MS (FAB)  $m/z$ : 469  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 471  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{23}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}\cdot\text{HCl}\cdot 0.4\text{H}_2\text{O}$

15 Calculated: C, 53.89; H, 4.48; N, 10.93; Cl, 13.83; S, 6.26.

Found: C, 53.95; H, 4.47; N, 11.02; Cl, 13.91; S, 6.39.

[Example A-69] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[2-  
 20 methyl-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Referential Example 7, a reaction was conducted using 1-(4-bromo-2-methylbenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material, whereby the title compound was obtained.

25  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.20(3H,s), 2.80-4.00(8H,m),

7.36 (1H, d, J=8.3Hz), 7.73 (1H, dd, J=8.8, 2.4Hz), 7.75-  
 7.85 (2H, m), 7.88 (1H, s), 8.18 (1H, d, J=8.8Hz), 8.20-  
 8.30 (4H, m), 8.50 (1H, br s), 8.90 (2H, d, J=6.8Hz).  
 MS (FAB) m/z: 506 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 508 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example A-70] 4-[4-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-3-methylphenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was  
 conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[2-  
 10 methyl-4-(pyridin-4-yl)benzoyl]piperazine as a starting  
 material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 2.27 (3H, s), 2.80-4.20 (8H, m),  
 7.16 (1H, d, J=8.3Hz), 7.38 (1H, J=8.3Hz), 7.41 (1H, br s),  
 7.48 (2H, d, J=6.8Hz), 7.61 (1H, dd, J=8.8, 1.5Hz),  
 15 7.75 (1H, d, J=8.8Hz), 7.91-7.97 (3H, m), 8.28 (2H, d, J=6.8Hz),  
 8.31 (1H, br s).

MS (FAB) m/z: 522 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 524 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>4</sub>S·H<sub>2</sub>O

Calculated: C, 60.05; H, 4.85; Cl, 6.56; N, 7.78; S, 5.94.

20 Found: C, 59.98; H, 4.89; Cl, 6.51; N, 7.48; S, 5.92.

[Example A-71] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-methyl-4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was  
 conducted using 3-methyl-4-(4-pyridyl)benzoic acid  
 25 hydrochloride as a starting material, whereby the title  
 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.27(3H,s), 3.08(4H,br), 3.47(2H,br),  
 3.72(2H,br), 7.26-7.37(3H,m), 7.73(1H,dd,J=8.8,2.0Hz),  
 7.83(1H,dd,J=8.8,2.0Hz), 7.86(2H,d,J=6.8Hz),  
 8.18(1H,d,J=8.8Hz), 8.25-8.29(2H,m), 8.50(1H,br s),  
 5 8.87(2H,d,J=6.8Hz).

MS (FAB) m/z: 506 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 508 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>3</sub>S·0.9HCl·1.7H<sub>2</sub>O

Calculated: C, 56.95; H, 5.01; Cl, 11.83; N, 7.38; S, 5.63.

Found: C, 57.08; H, 5.04; Cl, 11.75; N, 7.37; S, 5.49.

10 [Example A-72] 4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-piperazin-1-yl]carbonyl]-2-methylphenyl]pyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[3-methyl-4-(pyridin-4-yl)benzoyl piperazine as a starting  
 15 material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.28(3H,s), 3.13(4H,br), 3.63(2H,br),  
 3.86(2H,br), 7.15-7.28(5H,m), 7.60(1H,d,J=8.8Hz),  
 7.76(1H,d,J=8.8Hz), 7.90-7.96(3H,m), 8.26(2H,d,J=6.8Hz),  
 20 8.31(1H,s).

MS (FAB) m/z: 522 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 524 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>4</sub>S·H<sub>2</sub>O

Calculated: C, 60.05; H, 4.85; Cl, 6.56; N, 7.78; S, 5.94.

Found: C, 59.71; H, 4.68; Cl, 6.87; N, 7.63; S, 5.91.

25 [Example A-73] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-

(2-methylpyridin-4-yl)benzoyl]piperazine hydrochloride

In the same manner as in Example A-4, a reaction was conducted using 4-(2-methyl-4-pyridyl)benzoic acid hydrochloride as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.76(3H,s), 3.00-3.90(8H,m),  
7.56(2H,d,J=8.3Hz), 7.74(1H,dd,J=8.8,2.4Hz),  
7.38(1H,dd,J=8.8,2.0Hz), 8.00(2H,d,J=8.3Hz),  
8.14(1H,d,J=6.4Hz), 8.19(1H,d,J=8.8Hz), 8.22-8.29(3H,m),  
8.51(1H,br s), 8.80(1H,d,J=6.4Hz).

MS (FAB) m/z: 506 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 508 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·2H<sub>2</sub>O

Calculated: C, 56.06; H, 5.05; Cl, 12.26; N, 7.26; S, 5.54.

Found: C, 55.84; H, 5.03; Cl, 12.26; N, 6.87; S, 5.54.

[Example A-74] 4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, a reaction was conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.58(3H,s), 3.13(4H,br), 3.65(2H,br),  
3.84(2H,br), 7.34(1H,dd,J=6.8,2.4Hz), 7.41(2H,d,J=8.3Hz),  
7.45(1H,d,J=2.4Hz), 7.56-7.62(3H,m),  
7.76(1H,dd,J=8.8,2.0Hz), 7.91-7.96(3H,m), 8.28-8.32(2H,m).

MS (FAB) m/z: 522 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 524 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>4</sub>S·H<sub>2</sub>O·0.05CH<sub>2</sub>Cl<sub>2</sub>

Calculated: C, 59.69; H, 4.83; Cl, 7.16; N, 7.72; S, 5.89.

Found: C, 59.47; H, 4.87; Cl, 6.98; N, 7.48; S, 6.10.

5 [Example A-75] 4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[2-(morpholin-4-yl)ethylamino]carbonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-4, a reaction was  
10 conducted using 4-[4-[[2-carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide and 4-(2-aminoethyl)morpholine as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.22(4H,s), 2.35-2.80(6H,br), 3.20-  
15 3.90(3H,br), 3.74(4H,s), 4.20-4.60(1H,br), 5.25-5.50(1H,br), 6.80-7.20(1H,br), 7.45-7.70(7H,m), 7.76(1H,d,J=8.8Hz), 7.85-7.95(3H,m), 8.26(2H,d,J=6.9Hz), 8.32(1H,s).

MS (FAB) m/z: 664 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 666 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example A-76] 4-4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(dimethylamino)ethylamino]carbonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-4, a reaction was  
25 conducted using 4-[4-[[2-carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

and 2-(dimethylamino)ethylamine as starting materials,  
whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.29(6H,s), 2.35-2.75(6H,br), 3.35-  
3.90(3H,br), 4.40-4.60(1H,br), 5.25-5.50(1H,br), 7.00-  
5 7.20(1H,br), 7.45-7.65(7H,m), 7.77(1H,dd,  $J=8.8, 1.4\text{Hz}$ ),  
7.85-7.95(3H,m), 8.26(2H,d,  $J=7.3\text{Hz}$ ), 8.34(1H,s).

MS (FAB)  $m/z$ : 622  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 624  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ .

Elementary analysis for  $\text{C}_{31}\text{H}_{32}\text{N}_5\text{O}_5\text{S}\cdot 0.05\text{CH}_2\text{Cl}_2\cdot 2\text{H}_2\text{O}$

Calculated: C, 56.30; H, 5.49; N, 10.57; Cl, 5.89; S, 4.84.

10 Found: C, 56.27; H, 5.37; N, 10.39; Cl, 6.01; S, 4.91.

[Example A-77] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
methoxycarbonylmethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine

In the same manner as in Example A-68, a reaction was  
conducted using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-  
15 methoxycarbonylmethylpiperazine (723 mg) and 4-(2-  
pyridyl)benzoic acid hydrochloride as starting materials,  
whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ : 2.30-4.50(11H,m), 5.06(1H,br s), 7.30-  
7.50(3H,m), 7.72(1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.80-7.85(1H,m), 7.85-  
20 7.95(1H,m), 7.98(1H,d,  $J=7.8\text{Hz}$ ), 8.10(2H,d,  $J=8.3\text{Hz}$ ),  
8.18(1H,d,  $J=8.8\text{Hz}$ ), 8.25-8.30(2H,m), 8.51(1H,s), 8.65-  
8.70(1H,m).

MS (FAB)  $m/z$ : 564  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 566  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ .

Elementary analysis for  $\text{C}_{29}\text{H}_{26}\text{ClN}_3\text{O}_5\text{S}\cdot 1.1\text{H}_2\text{O}$

25 Calculated: C, 59.66; H, 4.87; N, 7.20; Cl, 6.07; S, 5.49.

Found: C, 59.53; H, 4.61; N, 7.05; Cl, 6.33; S, 5.70.

[Example A-78] 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-carboxymethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

5 In the same manner as in Example A-3, a reaction was conducted using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-methoxycarbonylmethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine as a starting material, whereby the title compound was obtained.

10  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.30-4.50 (8H, m), 5.05 (1H, br s), 7.35-7.40 (1H, m), 7.43 (2H, d,  $J=8.8\text{ Hz}$ ), 7.72 (1H, d,  $J=8.3\text{ Hz}$ ), 7.81 (1H, d,  $J=8.8\text{ Hz}$ ), 7.85-7.90 (1H, m), 7.97 (1H, d,  $J=7.8\text{ Hz}$ ), 8.08 (2H, d,  $J=8.8\text{ Hz}$ ), 8.17 (1H, d,  $J=8.8\text{ Hz}$ ), 8.25-8.30 (2H, m), 8.49 (1H, s), 8.65-8.70 (1H, m).

15 MS (FAB)  $m/z$ : 550  $[(M+H)^+, \text{Cl}^{35}]$ , 552  $[(M+H)^+, \text{Cl}^{35}]$ .

Elementary analysis for  $\text{C}_{28}\text{H}_{24}\text{ClN}_3\text{O}_5\text{S} \cdot 0.4\text{HCl} \cdot 0.9\text{H}_2\text{O}$

Calculated: C, 57.90; H, 4.55; N, 7.23; Cl, 8.55; S, 5.52.

Found: C, 57.76; H, 4.26; N, 7.02; Cl, 8.44; S, 5.27.

[Example A-79] 2-Carbamoylmethyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-2-yl)benzoyl]piperazine  
20 hydrochloride

In the same manner as in Example A-35, a reaction was conducted using 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-carboxymethyl-1-[4-(pyridin-2-yl)benzoyl]piperazine as a  
25 starting material, whereby the title compound was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.20-4.50 (8H, m), 5.10 (1H, br s),

6.96(2H,br s), 7.45-7.55(3H,m), 7.70-7.85(3H,m), 8.05-8.35(6H,m), 8.50(1H,s), 8.81(1H,d,J=4.9Hz).

MS (FAB) m/z: 549 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 551 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for C<sub>28</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>4</sub>S·1.3HCl·1.5H<sub>2</sub>O

5 Calculated: C, 53.94; H, 4.74; N, 8.99; Cl, 13.08; S, 5.14.

Found: C, 53.85; H, 4.87; N, 8.80; Cl, 13.19; S, 5.27.

[Example A-80] 1-[(Z)-4-Chloro-β-(2-hydroxyethan-1-yl)-β-styrylsulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

10 Under ice cooling, 4-tert-butoxycarbonyl-1-[(Z)-4-chloro-β-[2-(methoxymethyloxy)ethyl]-β-styrylsulfonyl]piperazine (355 mg) was dissolved in ethanol (3 ml), followed by the addition of saturated solution of hydrochloride (6 ml) in ethanol. The resulting mixture was stirred at room temperature for 1 hour. After the reaction mixture was concentrated under reduced pressure, a reaction was effected in the same manner as in Example A-4 by using the resulting residue, whereby the title compound (285 mg, 65%) was obtained.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.58(2H,t,J=6.6Hz), 3.06(4H,br s), 3.15-3.60(4H,br), 3.68(2H,t,J=6.6Hz), 7.24(1H,s), 7.38(2H,d,J=8.6Hz), 7.40(2H,d,J=8.6Hz), 7.47-7.57(3H,m), 8.02-8.10(2H,m), 8.14(2H,d,J=8.3Hz), 8.74(1H,d,J=4.4Hz). MS (FAB) m/z: 512 (M+H)<sup>+</sup>.

25 [Example A-81] 1-[(E)-4-Chloro-β-(2-hydroxyethan-1-yl)-β-



styrylsulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine  
hydrochloride

In the same manner as in Example A-80, the title  
compound (240 mg, 74%) was obtained using 4-tert-

5 butoxycarbonyl-1-[(E)-4-chloro- $\beta$ -(2-(methoxymethoxy)ethyl)- $\beta$ -styrylsulfonyl]piperazine (355  
mg) as a starting material.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.74 (2H, t,  $J=7.3\text{Hz}$ ), 3.27 (4H, br s),  
3.37-3.85 (6H, m), 7.45 (1H, s), 7.50-7.60 (5H, m),  
10 7.68 (2H, d,  $J=8.3\text{Hz}$ ), 8.06-8.17 (4H, m), 8.75 (1H, d,  $J=4.9\text{Hz}$ ).

MS (FAB)  $m/z$ : 512 ( $M+H$ ) $^+$ .

Elementary analysis for  $\text{C}_{26}\text{H}_{26}\text{ClN}_3\text{O}_4\text{S}\cdot 1.1\text{HCl}\cdot 0.8\text{H}_2\text{O}$

Calculated: C, 55.12; H, 5.11; N, 7.42; Cl, 13.14; S, 5.66.

Found: C, 55.22; H, 5.21; N, 7.20; Cl, 12.97; S, 5.66.

15 In the same manner as in Example A-7 or Example A-1,  
the compounds shown in Examples A-82 to A-86 were  
synthesized.

[Example A-82] 1-[(6-Chloro-1-phenylsulfonylindol-2-  
y)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.80-4.30 (8H, br), 7.34 (1H, d,  $J=8.5, 1.7\text{Hz}$ ),  
7.43-7.62 (9H, m), 7.69 (2H, d,  $J=7.8\text{Hz}$ ), 8.04 (2H, d,  $J=7.8\text{Hz}$ ),  
8.33 (1H, s), 8.70 (2H, br s).

Elementary analysis for  $\text{C}_{30}\text{H}_{25}\text{ClN}_4\text{O}_5\text{S}_2$

Calculated: C, 58.01; H, 4.06; Cl, 5.71; N, 9.02; S, 10.32.

25 Found: C, 58.34; H, 4.23; Cl, 5.78; N, 8.85; S, 9.96.

[Example A-83] 1-[(5-Chloro-3-methylbenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.67(3H,s), 3.15-3.31(4H,br), 3.37-3.84(4H,br), 7.58(1H,m), 7.65(1H,dd,J=8.8,2.0Hz), 7.92-8.03(2H,br), 8.13(1H,d,J=2.0Hz), 8.15-8.24(4H,m), 8.79-8.92(2H,br).

MS (FAB) m/z: 512 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 514 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S<sub>2</sub> · HCl · 0.3H<sub>2</sub>O

Calculated: C, 54.21; H, 4.29; Cl, 12.80; N, 7.59; S, 11.58.

Found: C, 54.25; H, 4.25; Cl, 12.98; N, 7.52; S, 11.52.

[Example A-84] 1-[(1-Phenylsulfonyl-5-trimethylsilylethynylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.25(9H,s), 3.35-4.00(8H,m), 7.43(2H,t,J=8.1Hz), 7.47-7.64(7H,m), 7.64-7.74(3H,m), 8.00(2H,d,J=8.1Hz), 8.23(1H,d,J=8.8Hz), 8.71(2H,br s).

[Example A-85] 1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.20-3.55(6H,br), 3.60-3.90(2H,br), 7.61(1H,dd,J=8.8,2.0Hz), 7.61(2H,d,J=8.8Hz), 7.68(1H,s), 7.84(1H,d,J=8.8Hz), 7.94(1H,d,J=2.0Hz), 8.05(2H,d,J=8.8Hz), 8.34(2H,d,J=5.9Hz), 8.95(2H,d,J=5.9Hz).

MS (FAB) m/z: 482 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 484 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot 0.6H_2O$

Calculated: C, 54.47; H, 4.23; Cl, 13.40; N, 7.94; S, 6.06.

Found: C, 54.48; H, 4.14; Cl, 13.41; N, 7.83; S, 6.17.

[Example A-86] 1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-  
5 [4-(pyridin-4-yl)benzoyl]piperazine

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.20-3.45 (4H, br), 3.35-3.55 (2H, br),  
3.65-3.85 (2H, br), 7.48 (1H, d,  $J=8.8$  Hz), 7.59 (2H, d,  $J=7.8$  Hz),  
7.73 (1H, s), 7.80-8.10 (1H, m), 7.86 (1H, d,  $J=8.8$  Hz),  
7.98 (1H, s), 8.04 (2H, d,  $J=7.8$  Hz), 8.20-8.32 (1/2H, m), 8.60-  
10 9.49 (1H, br), 8.90-8.93 (1/2H, m).

MS (FAB)  $m/z$ : 482  $[(M+H)^+, Cl^{35}]$ , 484  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot 0.3H_2O$

Calculated: C, 55.03; H, 4.16; Cl, 13.54; N, 8.02; S, 6.12.

Found: C, 55.06; H, 4.12; Cl, 13.62; N, 7.89; S, 6.11.

15 In the same manner as in Example A-7 or Example A-4,  
the compounds shown in Examples A-87 to A-93 were  
synthesized.

[Example A-87] 1-[(5-Chloro-1-phenylsulfonylindol-2-  
yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

20  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 3.45-3.53 (4H, br), 3.53-3.98 (4H, br), 7.40-  
7.50 (4H, m), 7.52-7.60 (6H, m), 7.70 (2H, d,  $J=8.3$  Hz),  
8.01 (2H, d,  $J=8.3$  Hz), 8.24 (1H, d,  $J=9.3$  Hz), 8.73 (2H, br).

MS (FAB)  $m/z$ : 621  $[(M+H)^+, Cl^{35}]$ , 623  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{30}H_{25}ClN_4O_5S_2 \cdot 0.1CH_2Cl_2$

25 Calculated: C, 57.42; H, 4.03; Cl, 6.76; N, 8.90; S, 10.19.

Found: C, 57.10; H, 4.35; Cl, 6.58; N, 8.80; S, 10.04.

[Example A-88] 1-[(1-Phenylsulfonyl-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.43-3.53(4H,br), 3.53-3.94(4H,br),  
 5 7.43(1H,t,J=7.6Hz), 7.40-7.46(2H,m), 7.48-7.65(10H,m),  
 7.69(2H,d,J=8.3Hz), 8.04(3H,m), 8.30(1H,d,J=8.3Hz),  
 8.69(2H,m).

MS (FAB) m/z: 587 (M+H)<sup>+</sup>

Elementary analysis for C<sub>30</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub>S<sub>2</sub>·0.5H<sub>2</sub>O

10 Calculated: C, 60.49; H, 4.57; N, 9.41; S, 10.77.

Found: C, 60.32; H, 4.73; N, 9.41; S, 10.43.

[Example A-89] 1-[(1-Phenylsulfonyl-5-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]homopiperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.85-1.92(1H,m), 2.13-2.20(1H,m), 3.47-  
 15 3.76(1H,m), 3.54-3.73(5H,m), 3.87-3.98(2H,m), 7.38-  
 7.60(11H,m), 7.69(2H,d,J=6.8Hz), 8.02-8.08(2H,m), 8.18-  
 8.23(1H,m), 8.69(2H,d,J=5.9Hz).

MS (FAB) m/z: 635 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 637 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example A-90] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.92-3.26(4H,br), 3.35-3.78(4H,br),  
 7.03(1H,d,J=2.0Hz), 7.34(1H,dd,J=8.8,2.4Hz), 7.47-  
 7.56(4H,m), 7.80(1H,d,J=2.0Hz), 8.02-8.16(4H,m),  
 8.73(1H,d,J=4.9Hz), 12.40(1H,s).

25 MS (FAB) m/z: 481 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 483 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{24}H_{21}ClN_4O_3S \cdot 0.9HCl \cdot 1.6H_2O$

Calculated: C, 53.13; H, 4.66; Cl, 12.41; N, 10.33; S, 5.91.

Found: C, 53.29; H, 4.89; Cl, 12.40; N, 10.15; S, 5.92.

[Example A-91] 1-[(5-Chloro-1-methylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 3.09-3.45(4H,br), 3.49-4.03(4H,br), 3.70(3H,s), 7.08(1H,m), 7.33(1H,d,J=8.8Hz), 7.37(2H,d,J=7.8Hz), 7.44-7.53(3H,m), 7.64-7.69(3H,m), 8.69(2H,br).

MS (FAB) m/z: 495  $[(M+H)^+, Cl^{35}]$ , 497  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{25}H_{23}ClN_4O_3S \cdot 0.1HCl \cdot 0.2H_2O$

Calculated: C, 56.12; H, 4.60; Cl, 13.25; N, 10.47; S, 5.99.

Found: C, 56.13; H, 4.54; Cl, 13.25; N, 10.40; S, 5.99.

[Example A-92] 1-[(5-Chloro-1-ethylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

$^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 1.30(3H,t,J=6.8Hz), 3.15-3.37(4H,br), 3.38-3.57(2H,br), 3.65-3.87(2H,br), 4.47(2H,q,J=6.8Hz), 7.17(1H,s), 7.41(1H,dd,J=8.8,2.0Hz), 7.63(2H,d,J=8.3Hz), 7.73(1H,d,J=8.8Hz), 7.81(1H,d,J=2.0Hz), 8.05(2H,d,J=8.3Hz), 8.31(2H,d,J=6.4Hz), 8.94(2H,d,J=6.4Hz).

MS (FAB) m/z: 509  $[(M+H)^+, Cl^{35}]$ , 511  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{26}H_{25}ClN_4O_3S \cdot 1.1HCl \cdot 1.2H_2O$

Calculated: C, 54.71; H, 5.03; Cl, 13.04; N, 9.82; S, 5.62.

Found: C, 54.51; H, 5.11; Cl, 13.06; N, 9.68; S, 5.71.

[Example A-93] 1-[(5-Chloro-1-ethoxycarbonylmethylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.19(3H,t,J=6.8Hz), 3.00-3.29(4H,br),  
3.30-3.85(4H,br), 4.14(2H,q,J=6.8Hz), 5.30(2H,s), 7.17-  
7.27(1H,m), 7.42(1H,d,J=8.8Hz), 7.59(2H,d,J=7.8Hz),  
7.73(1H,d,J=8.8Hz), 7.84(1H,s), 8.01(2H,d,J=7.8Hz),  
8.21(2H,d,J=6.3Hz), 8.88(2H,d,J=6.3Hz).

MS (FAB) m/z: 567 [(M+H) $^+$ , Cl $^{35}$ ], 569 [(M+H) $^+$ , Cl $^{37}$ ].

Elementary analysis for  $C_{28}H_{27}ClN_4O_5S \cdot 0.9HCl \cdot 0.5H_2O$

Calculated: C, 55.23; H, 4.78; Cl, 11.06; N, 9.20; S, 5.27.

Found: C, 54.91; H, 5.06; Cl, 10.78; N, 9.22; S, 5.45.

In the same manner as in Example A-4, the compounds shown in Examples A-94 to A-98 were synthesized.

[Example A-94] 1-[(5-Chlorobenzothiazol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.28-3.90(8H,m), 7.61(2H,d,J=8.3Hz),  
7.77(1H,dd,J=8.8,2.0Hz), 8.04(2H,d,J=8.8Hz),  
8.28(2H,d,J=6.4Hz), 8.38(1H,d,J=8.8Hz), 8.43(1H,d,J=2.0Hz),  
8.93(2H,d,J=6.4Hz).

MS (FAB) m/z: 499 [(M+H) $^+$ , Cl $^{35}$ ], 501 [(M+H) $^+$ , Cl $^{37}$ ].

Elementary analysis for  $C_{23}H_{19}ClN_4O_3S_2 \cdot HCl \cdot 0.6H_2O$

Calculated: C, 50.57; H, 3.91; Cl, 12.98; N, 10.26; S,

11.74.

Found: C, 50.72; H, 3.90; Cl, 13.22; N, 9.99; S,

11.35.

[Example A-95] 1-[(6-Chlorobenzothiazol-2-yl)sulfonyl]-4-

5 [4-(pyridin-4-yl)benzoyl]piperazine

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.28-3.90 (8H, m), 7.55 (2H, d,  $J=8.3\text{Hz}$ ),

7.77 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.85-7.93 (4H, m),

8.29 (1H, d,  $J=8.8\text{Hz}$ ), 8.50 (1H, d,  $J=2.0\text{Hz}$ ), 8.73 (2H, d,  $J=6.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 499  $[(M+H)^+, \text{Cl}^{35}]$ , 501  $[(M+H)^+, \text{Cl}^{37}]$ .

10 Elementary analysis for  $\text{C}_{23}\text{H}_{19}\text{ClN}_4\text{O}_3\text{S}_2 \cdot 0.25\text{HCl} \cdot 0.5\text{H}_2\text{O}$

Calculated: C, 53.42; H, 3.95; Cl, 8.57; N, 10.83; S,

12.40.

Found: C, 53.22; H, 3.91; Cl, 8.41; N, 10.70; S,

12.59.

15 [Example A-96] 1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-

[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.02-4.00 (8H, m), 7.51 (2H, d,  $J=8.8\text{Hz}$ ),

7.62 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.71 (2H, d,  $J=5.4\text{Hz}$ ),

7.82 (2H, d,  $J=8.8\text{Hz}$ ), 8.04 (1H, s), 8.17 (1H, d,  $J=2.0\text{Hz}$ ),

20 8.19 (1H, d,  $J=8.8\text{Hz}$ ), 8.65 (2H, d,  $J=5.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 498  $[(M+H)^+, \text{Cl}^{35}]$ , 499  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_3\text{S}_2 \cdot \text{HCl}$

Calculated: C, 53.93; H, 3.96; Cl, 13.27; N, 7.86; S,

12.00.

25 Found: C, 53.79; H, 4.07; Cl, 13.37; N, 7.70; S,

12.07.

[Example A-97] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.03-3.88 (8H, m), 7.56-7.61 (3H, m),

5 8.02 (2H, d,  $J=8.8\text{Hz}$ ), 8.09 (2H, d,  $J=8.8\text{Hz}$ ), 8.29 (2H, d,  $J=6.3\text{Hz}$ ),

8.34 (1H, d,  $J=2.0\text{Hz}$ ), 8.94 (2H, d,  $J=6.3\text{Hz}$ ).

MS (FAB)  $m/z$ : 498  $[(M+H)^+, \text{Cl}^{35}]$ , 500  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_3\text{S}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$

Calculated: C, 52.17; H, 4.20; Cl, 12.83; N, 7.61; S,

10 11.61.

Found: C, 52.18; H, 4.14; Cl, 12.84; N, 7.56; S,

11.70.

[Example A-98] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[4-(pyridin-2-yl)benzoyl]piperazine hydrochloride

15  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.02-3.90 (8H, m), 7.55 (2H, d,  $J=8.3\text{Hz}$ ),

7.58 (1H, dd,  $J=8.3, 1.5\text{Hz}$ ), 7.62 (1H, t,  $J=6.3\text{Hz}$ ), 8.07-

8.20 (6H, m), 8.33 (1H, d,  $J=1.5\text{Hz}$ ), 8.77 (1H, d,  $J=5.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 498  $[(M+H)^+, \text{Cl}^{35}]$ , 500  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_3\text{S}_2 \cdot \text{HCl} \cdot 0.8\text{H}_2\text{O}$

20 Calculated: C, 52.52; H, 4.15; Cl, 12.92; N, 7.66; S,

11.68.

Found: C, 52.69; H, 4.18; Cl, 12.63; N, 7.46; S,

11.68.

[Example A-99] 1-[(6-Chloroindol-2-yl)sulfonyl]-4-[4-

25 (pyridin-4-yl)benzoyl]piperazine



In tetrahydrofuran (4.0 ml), 1-[(1-phenylsulfonyl-6-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (380 mg) was dissolved, followed by the addition of methanol (4.0 ml) and potassium hydroxide (34.3 mg) at room temperature. The resulting mixture was stirred for 2 hours. To the reaction mixture, a saturated aqueous solution (30 ml) of ammonium chloride was added to make it weakly acidic. Then, a saturated aqueous solution (40 ml) of sodium bicarbonate was added to make the resulting mixture to weakly alkaline. The resulting mixture was added with dichloromethane (30 ml). The organic layer thus separated was extracted further with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure. The residue thus obtained was purified by preparative thin-layer chromatography on a silica gel (dichloromethane : acetone : methanol = 20:2:1), followed by recrystallization from a mixed solvent of hexane and dichloromethane, whereby the title compound (157 mg, 53%) was obtained as a white solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.70-4.20 (8H, br), 7.02 (1H, br s), 7.23 (1H, dd,  $J=8.3, 1.8\text{Hz}$ ), 7.42-7.50 (5H, m), 7.62-7.68 (3H, m), 8.69 (2H, d,  $J=5.9\text{Hz}$ ), 8.78 (1H, br s).

In the same manner as in Example A-99, the compounds shown in Examples A-100 to A-103 were synthesized.

[Example A-100] 1-[(Indol-2-yl)sulfonyl]-4-[4-(pyridin-4-

yl)benzoyl]piperazine

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.00-3.20 (4H, br), 3.42-3.84 (4H, br),  
7.05 (1H, s), 7.16 (1H, t,  $J=7.3\text{Hz}$ ), 7.33 (1H, m), 7.50 (3H, m),  
7.72 (2H, d,  $J=6.3\text{Hz}$ ), 7.82 (2H, d,  $J=7.8\text{Hz}$ ), 7.65 (2H, d,  $J=4.9\text{Hz}$ ),  
12.20 (1H, s).

MS (FAB)  $m/z$ : 447 ( $M+H$ ) $^+$

Elementary analysis for  $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_3\text{S}\cdot 0.2\text{H}_2\text{O}$

Calculated: C, 64.04; H, 5.02; N, 12.45; S, 7.12.

Found: C, 64.23; H, 5.30; N, 12.06; S, 7.07.

10 [Example A-101] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.94-3.25 (4H, br), 3.30-3.41 (4H, br),  
7.03 (1H, s), 7.33 (1H, d,  $J=8.8\text{Hz}$ ), 7.52 (1H, d,  $J=8.8\text{Hz}$ ),  
7.59 (2H, d,  $J=7.3\text{Hz}$ ), 7.80 (1H, s), 8.03 (2H, d,  $J=7.3\text{Hz}$ ),  
15 8.33 (2H, d,  $J=5.9\text{Hz}$ ), 8.95 (2H, d,  $J=5.9\text{Hz}$ ), 12.5 (1H, s).

MS (FAB)  $m/z$ : 481 [ $(M+H)^+$ ,  $\text{Cl}^{35}$ ], 483 [ $(M+H)^+$ ,  $\text{Cl}^{37}$ ].

Elementary analysis for  $\text{C}_{24}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}\cdot \text{HCl}\cdot 1.5\text{H}_2\text{O}$

Calculated: C, 52.95; H, 4.63; Cl, 13.02; N, 10.29; S, 5.89.

20 Found: C, 53.34; H, 4.74; Cl, 12.87; N, 9.92; S, 5.77.

[Example A-102] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]homopiperazine

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.75-1.85 (1H, br), 2.02-2.13 (1H, br),  
3.50-3.73 (6H, m), 3.92-3.96 (1H, br), 7.00 (1H, m), 7.28-  
25 7.35 (1H, m), 7.43-7.52 (2H, m), 7.58 (1H, d,  $J=7.8\text{Hz}$ ), 7.74-

7.78 (1H,m), 7.93-8.07 (2H,m), 8.14-8.36 (2H,m), 8.83-8.95 (2H,m), 12.43 (1H,m).

MS (FAB) m/z: 495 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 497 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>3</sub>S·1.05HCl·0.85H<sub>2</sub>O

5 Calculated: C, 54.73; H, 4.73; Cl, 13.25; N, 10.21; S, 5.85.

Found: C, 55.04; H, 5.03; Cl, 13.23; N, 9.89; S, 5.61.

[Example A-103] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.85-3.40 (4H,br), 3.06 (1H,s), 3.40-4.10 (4H,br), 7.01 (1H,br s), 7.39 (1H,d,J=8.8Hz), 7.45 (2H,d,J=8.3Hz), 7.45-7.50 (3H,m), 7.64 (2H,d,J=8.3Hz), 7.89 (1H,br s), 8.70 (2H,d,J=6.8Hz), 9.55 (1H,br s).

MS (FAB) m/z: 471 (M+H)<sup>+</sup>

15 [Example A-104] cis-4-[(5-Chloroindol-2-yl)sulfonyl]-2,6-dimethyl-1-[4-(pyridin-4-yl)benzoyl]piperazine

In tetrahydrofuran (50 ml), cis-1-(4-Bromobenzoyl)-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-1-(4-bromobenzoyl)-2,6-dimethylpiperazine (800 mg), diethyl 4-pyridylbolan (255 mg), tetrabutylammonium bromide (275 mg)  
20 and tetrakis(triphenylphosphine) palladium (0) (175 mg) were dissolved, followed by the addition of potassium hydroxide (289 mg) and water (0.745 ml). The resulting mixture was heated under reflux for 3 hours. The reaction  
25 mixture was concentrated under reduced pressure. Ethyl acetate and water were added to the residue to separate the

organic layer. The organic layer thus obtained was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by

5 chromatography on a silica gel column (2% methanol - dichloromethane), followed by crystallization from ethanol, whereby the title compound (580 mg, 53%) was obtained as colorless amorphous.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.33(6H,br), 2.60-2.70(2H,m), 3.40-  
10 3.60(2H,m), 3.70-4.10(1H,br), 4.40-4.90(1H,br), 7.02(1H,s), 7.30-7.35(1H,m), 7.45-7.55(3H,m), 7.72(2H,d,J=5.4Hz), 7.75-7.85(3H,m), 8.65(2H,d,J=5.4Hz), 12.43(1H,s).

Elementary analysis for C<sub>26</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>3</sub>S·0.3H<sub>2</sub>O

Calculated: C, 60.70; H, 5.02; Cl, 6.89; N, 10.89; S, 6.23.

15 Found: C, 61.03; H, 5.06; Cl, 7.09; N, 10.51; S, 6.09.

[Example A-105] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In a mixed solvent of dimethoxyethane (10 ml) and methanol (10 ml), 1-[(5-bromopyrimidin-2-yl)carbonyl]-4-  
20 [(5-chloroindol-2-yl)sulfonyl]piperazine (485 mg) and 4-pyridylboric acid (197 mg) were suspended at room temperature, followed by the successive addition of tetrakis(triphenylphosphine) palladium (0) (116 mg) and cesium fluoride (1.00 g). The resulting mixture was heated  
25 under reflux for 1 week. After the reaction mixture was cooled to room temperature, it was concentrated under

reduced pressure. Dichloromethane and water were added to the concentrate to separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (2% methanol - dichloromethane). The pale yellow crystals precipitated in ethanol were collected by filtration and dissolved in dichloromethane. To the resulting solution, 1N aqueous hydrochloride in ethanol was added and the resulting mixture was distilled under reduced pressure to remove the solvent. The yellow crystals precipitated in ethyl acetate were collected by filtration and dried, whereby the title compound (40%) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.96(2H,br s), 3.16(2H,br s), 3.38(2H,br s), 3.81(2H,br s), 7.05(1H,d,J=2.0Hz), 7.35(1H,dd,J=8.8,2.0Hz), 7.51(1H,d,J=8.8Hz), 7.81(1H,d,J=2.0Hz), 8.13(2H,d,J=5.9Hz), 8.87(2H,d,J=5.9Hz), 9.37(2H,s), 12.48(1H,s).

MS (FAB) m/z: 483 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 485 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>19</sub>ClN<sub>6</sub>O<sub>3</sub>S·0.9HCl·1.4H<sub>2</sub>O

Calculated: C, 48.84; H, 4.23; Cl, 12.45; N, 15.53; S, 5.93.

Found: C, 49.11; H, 4.27; Cl, 12.26; N, 15.34; S,

5.91.

In the same manner as in Example A-6, the compounds

shown in Examples A-106 to A-120 were synthesized.

[Example A-106] 4-[4-[[4-[(6-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.90-4.10(8H,br), 7.02(1H,d,J=1.0Hz),

5 7.22(1H,dd,J=8.8,1.7Hz), 7.46(2H,d,J=8.3Hz), 7.47(1H,s),

7.50(2H,d,J=7.3Hz), 7.60(2H,d,J=8.3Hz), 8.63(1H,d,J=8.8Hz),

8.29(2H,d,J=7.3Hz), 9.32(1H,br s).

Elementary analysis for C<sub>24</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S·1.7H<sub>2</sub>O

Calculated: C, 54.64; H, 4.66; Cl, 6.72; N, 10.62; S, 6.08.

10 Found: C, 54.63; H, 4.65; Cl, 6.91; N, 10.42; S, 6.07.

[Example A-107] 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.00-3.20(4H,br), 3.34-3.58(2H,br),

3.60-3.84(2H,br), 7.03(1H,s), 7.34(1H,d,J=8.8Hz),

15 7.47(2H,d,J=7.3Hz), 7.51(1H,d,J=8.8Hz), 7.79(2H,d,J=5.9Hz),

7.80(1H,s), 7.81(2H,d,J=7.3Hz), 8.28(2H,d,J=5.9Hz),

12.43(1H,br).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S·0.2H<sub>2</sub>O

20 Calculated: C, 57.59; H, 4.31; Cl, 7.08; N, 11.19; S, 6.41.

Found: C, 57.60; H, 4.38; Cl, 7.26; N, 11.09; S, 6.16.

[Example A-108] 4-[4-[[4-[(5-Chloro-1-methylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.06-3.45(4H,br), 3.48-4.06(4H,br),

25 4.00(3H,s), 7.07(1H,m), 7.33(1H,d,J=8.8Hz),

7.35 (2H, dd, J=8.8, 1.8 Hz), 7.45-7.57 (4H, m),

7.61 (2H, d, J=8.3 Hz), 7.66 (1H, d, J=2.0 Hz), 8.27 (2H, d, J=6.8 Hz).

MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>4</sub>S·0.9H<sub>2</sub>O·0.05CH<sub>2</sub>Cl<sub>2</sub>

5 Calculated: C, 56.61; H, 4.72; Cl, 7.34; N, 10.54; S, 6.03.

Found: C, 56.51; H, 4.71; Cl, 7.51; N, 10.37; S, 6.29.

[Example A-109] 2-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.04-3.18 (4H, br), 3.37-3.83 (4H, br),

10 7.03 (1H, s), 7.33 (1H, d, J=8.8 Hz), 7.38-7.44 (2H, m),

7.45 (2H, d, J=7.3 Hz), 7.50 (1H, d, J=8.8 Hz), 7.61-7.67 (1H, m),

7.80 (1H, s), 7.85 (2H, d, J=7.3 Hz), 8.33 (1H, m), 12.40 (1H, br).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S·0.2H<sub>2</sub>O

15 Calculated: C, 57.59; H, 4.31; Cl, 7.08; N, 11.19; S, 6.41.

Found: C, 57.72; H, 4.58; Cl, 7.13; N, 10.86; S, 6.29.

[Example A-110] 4-[4-[[4-[(5-Chloro-1-ethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.30 (3H, t, J=6.8 Hz), 3.18-3.38 (4H, br),

20 3.40-3.61 (2H, br), 3.62-3.84 (2H, br), 4.46 (2H, q, J=6.8 Hz),

7.16 (1H, s), 7.41 (1H, dd, J=8.8, 2.0 Hz), 7.52 (2H, d, J=7.3 Hz),

7.72 (1H, d, J=8.8 Hz), 7.78-7.88 (5H, m), 8.28 (2H, d, J=7.3 Hz).

MS (FAB) m/z: 525 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 527 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>4</sub>S·0.4H<sub>2</sub>O

25 Calculated: C, 58.67; H, 4.89; Cl, 6.66; N, 10.53; S, 6.02.

Found: C, 58.73; H, 4.91; Cl, 6.88; N, 10.26; S, 5.96.

[Example A-111] 4-[4-[[4-[(5-Chloro-3-methylbenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

5  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.67(3H,s), 3.12-3.29(4H,br), 3.37-3.86(4H,br), 7.48(2H,d,J=8.3Hz), 7.65(1H,dd,J=8.8,2.0Hz), 7.80(2H,d,J=7.3Hz), 7.81(2H,d,J=8.3Hz), 8.12(1H,d,J=2.0Hz), 8.15(1H,d,J=8.8Hz), 8.27(2H,d,J=7.3Hz).

MS (FAB)  $m/z$ : 528  $[(M+H)^+, \text{Cl}^{35}]$ , 530  $[(M+H)^+, \text{Cl}^{37}]$ .

10 Elementary analysis for  $\text{C}_{25}\text{H}_{22}\text{ClN}_3\text{O}_4\text{S}_2 \cdot 0.7\text{H}_2\text{O}$

Calculated: C, 55.54; H, 4.36; Cl, 6.56; N, 7.77; S, 11.86.

Found: C, 55.73; H, 4.40; Cl, 6.67; N, 7.52; S, 11.72.

[Example A-112] 4-[4-[[cis-4-[(5-Chloroindol-2-yl)sulfonyl]-2,6-dimethylpiperazin-1-

15 yl]carbonyl]phenyl]pyridine N-oxide

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.32(6H,br), 2.60-2.70(2H,m), 3.40-3.60(2H,m), 3.80-4.10(1H,br), 4.50-4.90(1H,br), 7.01(1H,s), 7.30-7.35(1H,m), 7.45-7.55(3H,m), 7.75-7.85(5H,m), 8.27(2H,d,J=6.8Hz), 12.44(1H,s).

20 Elementary analysis for  $\text{C}_{26}\text{H}_{25}\text{ClN}_4\text{O}_4\text{S} \cdot 0.5\text{H}_2\text{O}$

Calculated: C, 58.48; H, 4.91; Cl, 6.64; N, 10.49; S, 6.00.

Found: C, 58.68; H, 5.02; Cl, 6.72; N, 10.51; S, 6.04.

[Example A-113] 4-[4-[[4-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.20-3.50(4H,br), 3.50-4.05(4H,br),



7.34 (1H, s), 7.45-7.53 (6H, m), 7.62 (2H, d, J=7.8 Hz),  
7.69 (1H, s).

MS (FAB) m/z: 498 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 500 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>5</sub>S·0.25H<sub>2</sub>O

5 Calculated: C, 57.37; H, 4.11; Cl, 7.06; N, 8.36; S, 6.38.

Found: C, 57.31; H, 4.30; Cl, 7.17; N, 8.22; S, 6.40.

[Example A-114] 4-[4-[[4-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.20-3.50 (4H, br), 3.50-4.10 (4H, br), 3.65-  
10 3.85 (2H, br), 7.35-7.41 (2H, br), 7.46-7.55 (5H, br), 7.58-  
7.67 (5H, m), 8.27 (2H, d, J=5.9 Hz).

HRMS (FAB) m/z: 498.0901 (M+H)<sup>+</sup> (calcd for C<sub>24</sub>H<sub>21</sub>ClN<sub>3</sub>O<sub>5</sub>S  
498.0890).

[Example A-115] 4-[4-[[4-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide  
15

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.02-3.90 (8H, m), 7.59 (2H, d, J=8.3 Hz),  
7.64 (1H, d, J=2.0 Hz), 8.01-8.05 (3H, m), 8.18 (1H, d, J=2.0 Hz),  
8.20 (1H, d, J=8.8 Hz), 8.31 (2H, d, J=6.3 Hz), 8.94 (2H, d, J=6.3 Hz).

MS (FAB) m/z: 514 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 516 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>3</sub>S<sub>2</sub>·0.8H<sub>2</sub>O

Calculated: C, 54.55; H, 4.12; Cl, 6.71; N, 7.95; S, 12.14.

Found: C, 54.66; H, 4.09; Cl, 6.95; N, 7.77; S, 11.87.

[Example A-116] 4-[4-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.16-3.88 (8H, m), 7.48 (2H, d, J=8.3 Hz),

7.58 (1H, dd, J=8.8, 2.0Hz), 7.77 (1H, d, J=7.3Hz), 7.79 (1H, s),  
7.81 (2H, d, J=8.8Hz), 8.08 (2H, d, J=8.8Hz), 8.27 (1H, d, J=7.3Hz),  
8.33 (1H, s).

MS (FAB) m/z: 514 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 516 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>4</sub>S<sub>2</sub>·1.2H<sub>2</sub>O

Calculated: C, 53.82; H, 4.22; Cl, 6.62; N, 7.84; S, 11.97.

Found: C, 53.66; H, 4.22; Cl, 6.81; N, 7.61; S, 11.72.

[Example A-117] 2-[4-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.06-3.94 (8H, m), 7.38-7.42 (2H, m),  
7.46 (2H, d, J=8.3Hz), 7.54-7.63 (2H, m), 7.86 (2H, d, J=8.3Hz),  
8.07 (2H, t, J=4.4Hz), 8.27-8.34 (2H, m).

MS (FAB) m/z: 514 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 516 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>4</sub>S<sub>2</sub>·0.5H<sub>2</sub>O·0.1CH<sub>2</sub>Cl<sub>2</sub>

15 Calculated: C, 54.56; H, 4.01; Cl, 7.99; N, 7.89; S, 12.04.

Found: C, 54.93; H, 3.95; Cl, 7.90; N, 7.74; S, 11.71.

[Example A-118] 4-[4-[[4-[(5-Chlorobenzothiazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.40-4.00 (8H, m), 7.50 (2H, d, J=7.3Hz),  
7.51 (2H, d, J=8.3Hz), 7.58 (1H, dd, J=8.8, 2.0Hz),  
7.63 (2H, d, J=8.3Hz), 7.93 (1H, d, J=8.8Hz), 8.19 (1H, d, J=2.0Hz),  
8.27 (2H, d, J=7.3Hz).

MS (FAB) m/z: 515 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 517 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>23</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>4</sub>S<sub>2</sub>·0.1H<sub>2</sub>O

25 Calculated: C, 53.45; H, 3.74; Cl, 6.86; N, 10.84; S,

12.41.

Found: C, 53.19; H, 3.72; Cl, 7.09; N, 10.70; S,

12.29.

[Example A-119] 4-[4-[[4-[(6-Chlorobenzothiazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.30-3.85 (8H, m), 7.50 (2H, d, J=8.3 Hz), 7.77 (1H, dd, J=8.8, 2.0 Hz), 7.80 (2H, d, J=7.3 Hz), 7.83 (2H, d, J=8.3 Hz), 8.28 (2H, d, J=7.3 Hz), 8.29 (1H, d, J=8.8 Hz), 8.50 (1H, d, J=2.0 Hz).

MS (FAB) m/z: 515 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 517 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>23</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>4</sub>S<sub>2</sub>

Calculated: C, 53.64; H, 3.72; Cl, 6.88; N, 10.88; S,

12.45.

Found: C, 53.64; H, 3.99; Cl, 6.63; N, 10.90; S,

12.30.

[Example A-120] 4-[4-[[4-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.80-3.90 (8H, br), 4.05 (1H, s), 7.06 (1H, br s), 7.39 (1H, d, J=8.8 Hz), 7.43-7.52 (3H, m), 7.77-7.86 (4H, m), 7.89 (1H, br s), 8.27 (2H, d, J=6.8 Hz), 12.43 (1H, br s).

MS (FAB) m/z: 487 (M+H)<sup>+</sup>.

Elementary analysis for C<sub>26</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S·H<sub>2</sub>O

Calculated: C, 61.89; H, 4.79; N, 11.10; S, 6.36.

Found: C, 62.00; H, 4.67; N, 11.08; S, 6.35.

[Example A-121] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

In the same manner as in Example A-4, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.06(2H,br), 3.14(2H,br), 3.45-  
 5 3.85(4H,m), 7.74(1H,d,J=8.3Hz), 7.83(1H,d,J=8.8Hz),  
 8.19(1H,d,J=8.3Hz), 8.25-8.29(2H,m), 8.31(2H,d,J=5.9Hz),  
 8.52(1H,br s), 8.89(2H,d,J=5.9Hz), 9.02(2H,s).

MS (FAB) m/z: 494 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 496 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>3</sub>S·HCl·H<sub>2</sub>O

10 Calculated: C, 52.56; H, 4.23; Cl, 12.93; N, 12.77; S,  
 5.85.

Found: C, 52.47; H, 4.20; Cl, 13.09; N, 12.60; S,  
 5.98.

[Example A-122] 4-[5-[[4-[(6-Chloronaphthalen-2-  
 15 yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine  
 N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.05-3.30(4H,br), 3.55-4.00(4H,br),  
 20 7.61(1H,dd,J=8.3 and 2.0Hz), 7.76(1H,dd,J=8.8 and 2.0Hz),  
 7.91-7.97(3H,m), 8.25-8.29(2H,m), 8.31-8.35(3H,m),  
 8.77(2H,s).

MS (FAB) m/z: 510 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 512 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>4</sub>S·0.8H<sub>2</sub>O

25 Calculated: C, 54.97; H, 4.15; Cl, 6.76; N, 13.36; S, 6.11.

Found: C, 54.99; H, 4.08; Cl, 6.75; N, 13.24; S, 6.20.

[Example A-123] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-105, the title  
5 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.94(2H, br s), 3.13(2H, br s),  
3.37(2H, br s), 3.80(2H, br s), 7.74(1H, dd, J=8.8, 2.4Hz),  
7.83(1H, dd, J=8.8, 2.0Hz), 8.05-8.18(2H, br),  
8.19(1H, d, J=8.8Hz), 8.25-8.32(2H, m), 8.52(1H, br s), 8.82-  
10 8.91(2H, br), 9.33-9.38(2H, m).

MS (FAB) m/z: 494 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 496 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>3</sub>S·0.95HCl·0.5H<sub>2</sub>O

Calculated: C, 53.62; H, 4.12; Cl, 12.86; N, 13.03; S,  
5.96.

15 Found: C, 53.50; H, 4.09; Cl, 12.76; N, 12.87; S,  
5.91.

[Example A-124] 4-[2-[[4-[(6-Chloronaphthalen-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine  
N-oxide

20 In the same manner as in Example A-6, the title  
compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.14-3.17(2H, m), 3.25-3.28(2H, m), 3.55-  
3.58(2H, m), 3.94-3.98(2H, m), 7.50(2H, d, J=7.3Hz),  
7.60(1H, dd, J=8.8, 2.0Hz), 7.76(1H, dd, J=8.8, 2.0Hz), 7.91-  
25 7.96(3H, m), 8.30-8.35(3H, m), 8.98(2H, s).

MS (FAB)  $m/z$ : 510  $[(M+H)^+, Cl^{35}]$ , 512  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{24}H_{20}ClN_5O_4S \cdot 0.6H_2O$

Calculated: C, 55.35; H, 4.10; Cl, 6.81; N, 13.45; S, 6.16.

Found: C, 55.01; H, 4.01; Cl, 7.00; N, 13.28; S, 6.28.

5 [Example A-125] 4-[4-[[4-[(6-Bromonaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-1, the title compound was obtained using 4-[4-[(piperazin-1-yl)carbonyl]phenyl]pyridine N-oxide hydrochloride and (6-bromonaphthalen-2-yl)sulfonyl chloride as starting materials.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.80-3.40 (4H, br), 3.40-4.05 (4H, br), 7.43 (2H, d,  $J=7.8$  Hz), 7.47 (2H, d,  $J=7.1$  Hz), 7.58 (2H, d,  $J=7.8$  Hz), 7.70-7.78 (2H, m), 7.85 (1H, d,  $J=8.8$  Hz), 7.92 (1H, d,  $J=8.8$  Hz), 8.13 (1H, s), 8.26 (2H, d,  $J=7.1$  Hz), 8.30 (1H, s).

MS (FAB)  $m/z$ : 552  $[(M+H)^+, Br^{79}]$ , 554  $[(M+H)^+, Br^{81}]$ .

Elementary analysis for  $C_{26}H_{22}BrN_3O_4S \cdot 0.5H_2O$

Calculated: C, 55.62; H, 4.13; N, 7.48; Br, 14.23; S, 5.71.

Found: C, 55.36; H, 3.89; N, 7.41; Br, 14.20; S, 5.59.

20 [Example A-126] 1-[(6-Bromonaphthalen-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-1, a reaction was effected, whereby the title compound was obtained.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.80-3.40 (4H, br), 3.40-4.10 (4H, br), 7.43 (2H, d,  $J=8.3$  Hz), 7.47 (2H, d,  $J=5.6$  Hz), 7.63 (2H, d,  $J=8.3$  Hz),

7.72-7.78 (2H, m), 7.86 (1H, d, J=8.8 Hz), 7.92 (1H, d, J=8.8 Hz),  
8.13 (1H, d, J=1.5 Hz), 8.30 (1H, s), 8.68 (2H, d, J=5.6 Hz).

MS (FAB) m/z: 536 [(M+H)<sup>+</sup>, Br<sup>79</sup>], 538 [(M+H)<sup>+</sup>, Br<sup>81</sup>].

Elementary analysis for C<sub>26</sub>H<sub>22</sub>BrN<sub>3</sub>O<sub>3</sub>S·0.5H<sub>2</sub>O

5 Calculated: C, 57.25; H, 4.25; N, 7.70; Br, 14.65; S, 5.88.

Found: C, 57.51; H, 3.96; N, 7.67; Br, 14.76; S, 6.01.

[Example A-127] 1-[(6-Ethynylnaphthalen-2-yl)sulfonyl]-4-  
[4-(pyridin-4-yl)benzoyl]piperazine

To a solution of 1-[(6-bromonaphthalen-2-yl)sulfonyl]-  
10 4-[4-(pyridin-4-yl)benzoyl]piperazine (310 mg) and  
triphenylphosphine (455 mg) in tetrahydrofuran (1.0 ml),  
triethylamine (3.0 ml), N,N-dimethylformamide (1.0 ml),  
trimethylsilylacetylene (130 ml) and palladium acetate  
(13.0 mg) were added, followed by heating under reflux for  
15 2 hours. After the reaction mixture was allowed to cool  
down to room temperature, dichloromethane (15 ml) and water  
(30 ml) were added to separate the organic layer. The  
organic layer thus obtained was dried over anhydrous sodium  
sulfate and distilled under reduced pressure to remove the  
20 solvent. The residue was purified by chromatography on a  
silica gel column (dichloromethane : acetone = 3:1),  
whereby colorless amorphous was obtained. The resulting  
product was dissolved in methanol (25 ml), followed by the  
addition of tetrahydrofuran (5.0 ml) and potassium  
25 carbonate (300 mg). The resulting mixture was stirred for  
30 minutes. Dichloromethane (30 ml) and water (50 ml) were

added to the reaction mixture to separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified  
 5 by chromatography on a silica gel column (dichloromethane : acetone = 4:1), followed by pulverization and washing in a mixed solvent of dichloromethane, acetone and water, whereby the title compound (210 mg, 75%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.80-4.10 (8H, br), 7.43 (2H, d, J=8.3Hz),  
 10 7.47 (2H, d, J=6.4Hz), 7.67 (2H, d, J=8.3Hz),  
 7.68 (1H, dd, J=8.8, 1.5Hz), 7.75 (1H, dd, J=8.3, 1.5Hz),  
 7.93 (1H, d, J=8.3Hz), 7.97 (1H, d, J=8.8Hz), 8.11 (1H, s),  
 8.30 (1H, s), 8.68 (2H, d, J=6.4Hz).

MS (FAB) m/z: 482 (M+H)<sup>+</sup>.

15 Elementary analysis for C<sub>28</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>S·0.4H<sub>2</sub>O

Calculated: C, 68.81; H, 4.91; N, 8.60; S, 6.56.

Found: C, 68.96; H, 4.91; N, 8.47; S, 6.52.

[Example A-128] 4-[4-[[4-[(6-Ethynylnaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

20 In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.95-4.00 (8H, br), 7.42 (2H, d, J=8.3Hz),  
 7.46 (2H, d, J=6.8Hz), 7.58 (2H, d, J=8.3Hz),  
 7.68 (1H, dd, J=8.8, 1.5Hz), 7.75 (1H, dd, J=8.3, 1.5Hz),  
 25 7.92 (1H, d, J=8.8Hz), 7.95 (1H, d, J=8.3Hz), 8.10 (1H, s),



8.25 (2H, d, J=6.8 Hz), 8.30 (1H, s).

MS (FAB) m/z: 498 [(M+H)<sup>+</sup>].

Elementary analysis for C<sub>28</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>S·H<sub>2</sub>O

Calculated: C, 65.23; H, 4.89; N, 8.15; S, 6.22.

5 Found: C, 65.41; H, 5.14; N, 8.19; S, 6.11.

[Example A-129] 2-Carbamoylmethyl-4-[(5-chloro-1-phenylsulfonyl-5-chloroindol-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

10 In the same manner as in Example A-7 or Example A-1, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.44-3.28 (4H, m), 3.50-4.14 (2H, m), 4.45-4.78 (1H, m), 5.58-5.79 (1H, m), 7.44-7.65 (13H, m), 7.69 (2H, d, J=8.3 Hz), 8.05 (2H, d, J=8.3 Hz), 8.13-8.17 (1H, m), 15 8.69 (2H, d, J=5.9 Hz).

MS (FAB) m/z: 678 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 680 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-130] 2-Carbamoylmethyl-4-[(5-chloroindol-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

20 In the same manner as in Example A-99, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.55-2.80 (2H, m), 3.00-4.56 (6H, m), 5.05-5.17 (1H, m), 6.90-7.05 (2H, m), 7.34 (1H, dd, J=8.8, 2.2 Hz), 7.40-7.63 (4H, m), 7.79 (1H, m), 7.99 (1H, m), 8.24 (2H, br), 8.90 (1H, m), 12.43 (1H, s).

25 MS (FAB) m/z: 538 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 540 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{26}H_{24}ClN_5O_4S \cdot 1.2HCl \cdot 2.5H_2O$

Calculated: C, 49.82; H, 4.86; Cl, 12.44; N, 11.17; S, 5.12.

Found: C, 50.14; H, 5.07; Cl, 12.54; N, 10.80; S, 5.18.

[Example A-131] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

In the same manner as in Example A-4, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.08 (2H, br), 3.18 (2H, br), 3.52 (2H, br), 3.77 (2H, br), 7.04 (1H, d, J=1.5 Hz), 7.34 (1H, dd, J=8.8, 2.0 Hz), 7.50 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=2.0 Hz), 8.48-8.53 (2H, m), 8.91-8.95 (2H, m), 9.07 (2H, s), 12.46 (1H, br s).

MS (FAB) m/z: 483 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 485 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{22}H_{19}ClN_6O_3S \cdot HCl \cdot 1.3H_2O \cdot 0.2EtOH$   
Calculated: C, 48.74; H, 4.35; Cl, 12.84; N, 15.22; S, 5.81.

Found: C, 48.87; H, 4.38; Cl, 12.82; N, 15.02; S, 5.86.

[Example A-132] 1-[(6-Chlorobenzothiophen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-105, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.03-3.06 (2H, m), 3.20-3.23 (2H, m), 3.41-3.44 (2H, m), 3.83-3.86 (2H, m), 7.61 (1H, dd, J=8.8, 2.0 Hz),

8.10 (1H, d, J=8.8 Hz), 8.13 (1H, s), 8.30-8.40 (3H, m), 8.90-9.02 (2H, br), 9.40-9.46 (2H, m).

MS (FAB) m/z: 500 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 502 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>3</sub>S·HCl·0.7H<sub>2</sub>O

5 Calculated: C, 48.13; H, 3.74; Cl, 12.91; N, 12.75; S, 11.68.

Found: C, 47.95; H, 3.78; Cl, 13.13; N, 12.65; S, 11.53.

[Example A-133] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine  
10 N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.24 (2H, br), 3.34 (2H, br), 3.60 (2H, br),  
15 3.98 (2H, br), 7.47 (1H, dd, J=8.8, 2.0 Hz), 7.52 (2H, d, J=7.3 Hz), 7.79 (1H, s), 7.83 (1H, d, J=8.8 Hz), 7.88 (1H, br s), 8.33 (2H, d, J=7.3 Hz), 9.00 (2H, s).

MS (FAB) m/z: 516 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 518 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>4</sub>S·0.4H<sub>2</sub>O

20 Calculated: C, 50.50; H, 3.62; Cl, 6.78; N, 13.39; S, 12.26.

Found: C, 50.24; H, 3.62; Cl, 7.14; N, 13.19; S, 12.04.

[Example A-134] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine  
25 N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.95(2H,br), 3.15(2H,br), 3.37(2H,br), 3.79(2H,br), 7.05(1H,s), 7.34(1H,dd,J=8.8,1.5Hz),  
 5 7.51(1H,d,J=8.8Hz), 7.80(1H,d,J=1.5Hz), 7.95(2H,d,J=7.3Hz),  
 8.37(2H,d,J=7.3Hz), 9.28(2H,s), 12.47(1H,s).

MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>19</sub>ClN<sub>6</sub>O<sub>4</sub>S·0.5H<sub>2</sub>O·0.2EtOH

Calculated: C, 52.02; H, 4.13; Cl, 6.86; N, 16.25; S, 6.20.

10 Found: C, 52.03; H, 3.99; Cl, 7.18; N, 15.99; S, 6.16.

[Example A-135] 4-[5-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

15 In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.09(2H,br), 3.16(2H,br), 3.53(2H,br), 3.75(2H,br), 7.03(1H,s), 7.32(1H,dd,J=8.8,2.0Hz),  
 7.50(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz), 8.27(2H,d,J=7.3Hz),  
 8.34(2H,d,J=7.3Hz), 8.95(2H,s), 12.42(1H,br s).

20 MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>19</sub>ClN<sub>6</sub>O<sub>4</sub>S·H<sub>2</sub>O

Calculated: C, 51.11; H, 4.09; Cl, 6.86; N, 16.26; S, 6.20.

Found: C, 51.29; H, 4.34; Cl, 6.80; N, 15.90; S, 6.08.

[Example A-136] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine  
 25

In the same manner as in Example A-105, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.20 (2H, t,  $J=4.9\text{Hz}$ ), 3.62-3.78 (2H, m),  
3.45-3.60 (2H, m), 3.78 (2H, t,  $J=4.9\text{Hz}$ ), 4.63 (2H, s),  
5 4.64 (2H, s), 7.35 (1H, d,  $J=8.3\text{Hz}$ ), 7.38 (1H, d,  $J=8.3\text{Hz}$ ),  
7.42 (1H, s), 8.22 (2H, d,  $J=5.4\text{Hz}$ ), 8.92 (2H, d,  $J=5.4\text{Hz}$ ),  
9.44 (2H, s).

MS (FAB)  $m/z$ : 485  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 487  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{22}\text{H}_{21}\text{ClN}_6\text{O}_3\text{S}\cdot\text{HCl}\cdot 1.8\text{H}_2\text{O}$

10 Calculated: C, 47.71; H, 4.66; Cl, 12.80; N, 15.17; S,  
5.79.

Found: C, 48.01; H, 4.39; Cl, 13.19; N, 14.74; S,  
5.73.

In the same manner as in Example A-4, the compounds  
15 shown in Examples A-137 and A-138 were synthesized.

[Example A-137] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]piperazine

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.01 (2H, br), 3.14 (2H, br), 3.62 (2H, br),  
3.81 (2H, br), 7.74 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
20 7.84 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.19 (1H, d,  $J=8.8\text{Hz}$ ), 8.25-  
8.31 (2H, m), 8.46 (2H, d,  $J=5.4\text{Hz}$ ), 8.52 (1H, br s), 8.91 (3H, m),  
9.47 (1H, s).

MS (FAB)  $m/z$ : 494  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 496  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{24}\text{H}_{20}\text{ClN}_5\text{O}_3\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}\cdot 0.2\text{AcOEt}$

25 Calculated: C, 52.62; H, 4.38; Cl, 12.53; N, 12.37; S,

5.66.

Found: C, 52.47; H, 4.51; Cl, 12.87; N, 12.09; S,

5.68.

[Example A-138] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-  
5 (pyridin-4-yl)pyrazin-2-yl]carbonyl]piperazine

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.04 (2H, br), 3.18 (2H, br), 3.63 (2H, br),  
3.81 (2H, br), 7.05 (1H, s), 7.33 (1H, dd, J=8.8, 2.0 Hz),  
7.50 (1H, d, J=8.8 Hz), 7.79 (1H, d, J=2.0 Hz), 8.11 (2H, d, J=6.4 Hz),  
8.77 (2H, d, J=6.4 Hz), 8.93 (1H, d, J=1.5 Hz), 9.34 (1H, d, J=1.5 Hz),  
10 12.43 (1H, br s).

MS (FAB) m/z: 483 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 485 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>19</sub>ClN<sub>6</sub>O<sub>3</sub>S·H<sub>2</sub>O

Calculated: C, 52.75; H, 4.23; Cl, 7.08; N, 16.78; S, 6.40.

Found: C, 52.78; H, 4.27; Cl, 7.17; N, 16.67; S, 6.37.

15 In the same manner as in Example A-6, reaction was  
effected, whereby the compounds shown in Examples A-139 and  
A-140 were synthesized.

[Example A-139] 4-[5-[[4-[(6-Chloronaphthalen-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrazin-2-yl]pyridine

20 N-oxide

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.19 (2H, br), 3.26 (2H, br), 3.88 (2H, br),  
3.94 (2H, br), 7.59 (1H, dd, J=8.8, 2.0 Hz),  
7.78 (1H, dd, J=8.8, 2.0 Hz), 7.91-7.95 (3H, m),  
7.98 (2H, d, J=7.3 Hz), 8.30 (2H, d, J=7.3 Hz), 8.32 (1H, d, J=2.0 Hz),  
25 8.90 (1H, d, J=1.5 Hz), 8.99 (1H, d, J=1.5 Hz).

MS (FAB) m/z: 510 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 512 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>4</sub>S·1.1H<sub>2</sub>O

Calculated: C, 54.41; H, 4.22; Cl, 6.69; N, 13.22; S, 6.05.

Found: C, 54.27; H, 4.61; Cl, 6.99; N, 13.28; S, 6.12.

5 [Example A-140] 4-[5-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrazin-2-yl]pyridine N-oxide

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.03(2H,br), 3.17(2H,br), 3.63(2H,br),  
3.80(2H,br), 7.04(1H,s), 7.33(1H,dd,J=8.8,2.0Hz),  
10 7.50(1H,d,J=8.8Hz), 7.80(1H,d,J=2.0Hz), 8.19(2H,d,J=7.3Hz),  
8.37(2H,d,J=7.3Hz), 8.87(1H,d,J=1.5Hz), 9.31(1H,d,J=1.5Hz),  
12.45(1H,br s).

MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>19</sub>ClN<sub>6</sub>O<sub>4</sub>S·H<sub>2</sub>O

15 Calculated: C, 51.11; H, 4.09; Cl, 6.86; N, 16.26; S, 6.20.

Found: C, 50.92; H, 4.05; Cl, 6.96; N, 15.88; S, 6.10.

[Example A-141] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(3-methylpyridin-4-yl)benzoyl]piperazine hydrochloride

20 In the same manner as in Example A-4, a reaction was effected, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.36(3H,s), 2.95-3.30(4H,br), 3.35-  
3.90(4H,br), 7.50(2H,d,J=8.8Hz), 7.53(2H,d,J=8.8Hz),  
7.71(1H,d,J=5.4Hz), 7.73(1H,dd,J=8.8,2.0Hz),  
7.83(1H,dd,J=8.8,2.0Hz), 8.18(1H,d,J=8.8Hz), 8.24-  
25 8.30(2H,m), 8.50(1H,br s), 8.72(1H,d,J=5.4Hz), 8.80(1H,s).

MS (FAB)  $m/z$ : 506  $[(M+H)^+, Cl^{35}]$ , 508  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{27}H_{24}ClN_3O_3S \cdot 0.8HCl \cdot 1.5H_2O$

Calculated: C, 57.68; H, 4.98; Cl, 11.35; N, 7.48; S, 5.70.

Found: C, 57.50; H, 5.06; Cl, 11.35; N, 7.28; S, 5.95.

5 [Example A-142] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-3-methylpyridine N-oxide

In the same manner as in Example A-6, a reaction was effected, whereby the title compound was obtained.

10  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.21(3H,s), 3.14(4H,br), 3.68(2H,br), 3.85(2H,br), 7.09(1H,d,J=6.8Hz), 7.32(2H,d,J=8.3Hz), 7.41(2H,d,J=8.3Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.77(1H,dd,J=8.8,2.0Hz), 7.90-7.96(3H,m), 8.11(1H,dd,J=6.4,1.5Hz), 8.15(1H,br s), 8.31(1H,br s).

15 MS (FAB)  $m/z$ : 522  $[(M+H)^+, Cl^{35}]$ , 524  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{27}H_{24}ClN_3O_4S \cdot 0.1H_2O$

Calculated: C, 61.92; H, 4.66; Cl, 6.77; N, 8.02; S, 6.12.

Found: C, 61.76; H, 4.72; Cl, 7.04; N, 7.76; S, 6.30.

20 [Example A-143] 1-(4-Amidinobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Example A-4, a reaction was effected, whereby the title compound was obtained.

$^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 3.03(2H,br s), 3.13(2H,br s), 3.30(2H,br s), 3.73(2H,br s), 7.56(2H,d,J=8.3Hz),

25 7.73(1H,dd,J=8.8,2.0Hz), 7.78-7.85(3H,m),



8.18 (1H, d, J=8.3Hz), 8.25-8.30 (2H, m), 8.50 (1H, s), 9.10 (2H, br s), 9.38 (2H, br s).

MS (FAB) m/z: 457 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 459 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-144] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

5 [4-(4,5-dihydroimidazol-2-yl)benzoyl]piperazine

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.04 (2H, br s), 3.13 (2H, br s),

3.37 (2H, br s), 3.74 (2H, br s), 4.00 (4H, s),

7.60 (2H, d, J=8.3Hz), 7.73 (1H, dd, J=8.8, 2.0Hz),

7.83 (1H, d, J=8.8Hz), 8.11 (2H, d, J=8.3Hz), 8.19 (1H, d, J=8.8Hz),

10 8.26 (1H, d, J=2.0Hz), 8.28 (1H, d, J=8.8Hz), 8.50 (1H, s),

11.00 (2H, br s).

MS (FAB) m/z: 483 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 485 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-145] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[4-[2-(N-tert-butoxycarbonylamino)pyridin-4-

15 yl]benzoyl]piperazine

In the same manner as in Example A-4, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.54 (9H, s), 3.00-3.30 (4H, m), 3.40-

4.10 (4H, m), 7.14 (1H, dd, J=5.4, 1.5Hz), 7.38 (2H, d, J=8.3Hz),

20 7.53 (1H, br s), 7.60 (1H, dd, J=8.8, 2.0Hz), 7.67 (2H, d, J=8.3Hz),

7.77 (1H, dd, J=8.3, 1.5Hz), 7.91-7.98 (3H, m),

8.18 (1H, d, J=1.5Hz), 8.29 (1H, d, J=5.4Hz), 8.32 (1H, s).

[Example A-146] 1-[4-(2-Aminopyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

25 In the same manner as in Example A-7, the title

compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.95-3.25 (4H,m), 3.30-3.93 (4H,m), 7.14-7.23 (2H,m), 7.51 (2H,d,J=8.3Hz), 7.66-7.75 (1H,m), 7.76 (2H,d,J=8.8Hz), 7.82 (1H,m), 8.03 (1H,d,J=6.8Hz), 8.05-8.12 (2H,m), 8.13-8.30 (3H,m), 8.50 (1H,s), 13.60 (1H,br).  
 MS (FAB) m/z: 507 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 509 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>3</sub>S · HCl · 3.6H<sub>2</sub>O

Calculated: C, 51.34; H, 5.17; Cl, 11.66; N, 9.21; S, 5.27.

Found: C, 51.07; H, 5.24; Cl, 11.85; N, 9.10; S, 5.75.

10 [Example A-147] 2-tert-Butoxycarbonylamino-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.55 (9H,s), 2.95-3.35 (4H,br), 3.50-4.00 (4H,m), 7.11 (1H,dd,J=6.8,2.5Hz), 7.40 (2H,d,J=8.3Hz), 7.60 (1H,dd,J=8.8,2.0Hz), 7.64 (2H,d,J=8.3Hz), 7.77 (1H,dd,J=8.8,2.0Hz), 7.91-7.98 (3H,m), 8.25 (1H,d,J=6.8Hz), 8.31 (1H,d,J=2.0Hz), 8.42 (1H,d,J=2.5Hz),  
 20 9.28 (1H,s).

MS (FAB) m/z: 623 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 625 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>31</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>6</sub>S · 0.1H<sub>2</sub>O

Calculated: C, 59.58; H, 5.03; Cl, 5.67; N, 8.97; S, 5.13.

Found: C, 59.43; H, 5.04; Cl, 5.95; N, 8.89; S, 5.17.

25 [Example A-148] 2-Amino-4-[4-[[4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-7, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.95-3.25 (4H, br), 3.30-3.90 (4H, m),  
 5 7.14 (1H, dd, J=6.8, 2.0 Hz), 7.28 (1H, d, J=2.0 Hz),  
 7.49 (2H, d, J=8.3 Hz), 7.70-7.78 (3H, m),  
 7.82 (1H, dd, J=8.8, 2.0 Hz), 8.16 (2H, br), 8.18 (1H, d, J=8.8 Hz),  
 8.25-8.30 (2H, m), 8.32 (1H, d, J=6.8 Hz), 8.50 (1H, br s).

MS (FAB) m/z: 523 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 525 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 Elementary analysis for C<sub>26</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>4</sub>S·HCl·1.5H<sub>2</sub>O

Calculated: C, 53.25; H, 4.64; Cl, 12.09; N, 9.55; S, 5.47.

Found: C, 53.21; H, 4.67; Cl, 11.96; N, 9.53; S, 5.61.

[Example A-149] 4-[5-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyridin-2-yl]pyridine

15 N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.00-3.40 (4H, br s), 3.50-4.05 (4H, m),  
 7.61 (1H, dd, J=8.8, 2.0 Hz), 7.73-7.83 (3H, m), 7.90-7.97 (5H, m),  
 20 8.27 (2H, d, J=7.3 Hz), 8.31 (1H, br s), 8.63 (1H, m).

MS (FAB) m/z: 509 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 511 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S·0.5H<sub>2</sub>O

Calculated: C, 57.97; H, 4.28; Cl, 6.84; N, 10.82; S, 6.19.

Found: C, 57.99; H, 4.51; Cl, 6.99; N, 10.54; S, 6.53.

25 [Example A-150] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[[1-oxo-6-(1-oxopyridin-4-yl)pyridin-3-yl]carbonyl]piperazine

In the same manner as in Example A-6, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.15(4H, br s), 3.50-4.00(4H, m), 7.20-7.30(1H, m), 7.52(1H, d,  $J=8.3\text{Hz}$ ), 7.61(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.76(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.89(2H, d,  $J=7.3\text{Hz}$ ), 7.91-7.97(3H, m), 8.21(1H, d,  $J=1.5\text{Hz}$ ), 8.26(2H, d,  $J=7.3\text{Hz}$ ), 8.31(1H, br s).

10 MS (FAB)  $m/z$ : 525  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 527  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{25}\text{H}_{21}\text{ClN}_4\text{O}_5\text{S}\cdot 0.1\text{H}_2\text{O}$

Calculated: C, 57.00; H, 4.06; Cl, 6.73; N, 10.64; S, 6.09.

Found: C, 57.03; H, 4.23; Cl, 6.82; N, 10.34; S, 6.15.

[Example A-151] 1-[4-(2-Acetoxymethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
15 hydrochloride

In acetic anhydride (25 ml), 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide (900 mg) was  
20 dissolved, followed by heating under reflux for 15 minutes. Ethanol (25 ml) was added to the reaction mixture and the resulting mixture was heated under reflux for further 1 hour. To the reaction mixture, dichloromethane and an aqueous solution of sodium bicarbonate were added to  
25 separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate and

concentrated under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 1.5% methanol - dichloromethane), followed by crystallization from ethanol. The crystals  
 5 were dissolved in dichloromethane and the resulting solution was made acidic by the addition of hydrochloric acid in ethanol. The resulting acidic mixture was concentrated, whereby the title compound (842 mg, 87%, pale yellow powder) was obtained.

10  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.12(3H,s), 3.06(4H,br), 3.30-3.80(4H,br), 5.23(2H,s), 7.48(2H,d,J=8.3Hz), 7.72(1H,dd,J=8.8,2.4Hz), 7.78(1H,d,J=5.4Hz), 7.79-7.87(4H,m), 8.17(1H,d,J=8.8Hz), 8.23-8.29(2H,m), 8.49(1H,br s), 8.67(1H,d,J=5.4Hz).

15 MS (FAB)  $m/z$ : 564  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 566  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{29}\text{H}_{26}\text{ClN}_3\text{O}_5\text{S}\cdot 0.4\text{HCl}\cdot 0.7\text{H}_2\text{O}$

Calculated: C, 58.91; H, 4.74; Cl, 8.39; N, 7.11; S, 5.42.

Found: C, 58.86; H, 4.69; Cl, 8.29; N, 6.99; S, 5.41.

[Example A-152] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-hydroxymethylpyridin-4-yl)benzoyl]piperazine  
 20

In the same manner as in Example A-3, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.08(4H,br), 3.47(2H,br), 3.71(2H,br), 4.66(2H,s), 7.49(2H,d,J=8.3Hz), 7.64(1H,d,J=5.4Hz),  
 25 7.73(1H,dd,J=8.8,2.0Hz), 7.78-7.85(4H,m),

8.18 (1H, d, J=8.8Hz), 8.23-8.30 (2H, m), 8.50 (1H, br s),  
8.58 (1H, d, J=5.4Hz).

MS (FAB) m/z: 522 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 524 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>4</sub>S·0.25HCl·1.2H<sub>2</sub>O

5 Calculated: C, 58.67; H, 4.86; Cl, 8.02; N, 7.60; S, 5.80.

Found: C, 58.73; H, 4.77; Cl, 7.94; N, 7.39; S, 5.82.

[Example A-153] 2-Acetoxymethyl-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.21 (3H, s), 3.14 (4H, br), 3.30-4.10 (4H, br), 5.42 (2H, s), 7.40-7.46 (3H, m), 7.54-7.64 (4H, m), 7.76 (1H, d, J=7.3Hz), 7.90-7.97 (3H, m), 8.29 (1H, d, J=6.4Hz),  
15 8.31 (1H, br s).

MS (FAB) m/z: 580 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 582 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>29</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>6</sub>S·0.3H<sub>2</sub>O

Calculated: C, 59.49; H, 4.58; Cl, 6.06; N, 7.18; S, 5.48.

Found: C, 59.33; H, 4.63; Cl, 6.18; N, 7.26; S, 5.49.

20 [Example A-154] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-hydroxymethylpyridine N-oxide

In the same manner as in Example A-3, the title compound was obtained.

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.06 (4H, br), 3.30-3.90 (4H, br),

4.63 (2H, d, J=5.4 Hz), 5.66 (1H, t, J=5.4 Hz), 7.46 (2H, d, J=8.3 Hz),  
 7.70 (1H, dd, J=6.8, 2.9 Hz), 7.73 (1H, dd, J=8.8, 2.0 Hz),  
 7.78 (2H, d, J=8.3 Hz), 7.80-7.84 (2H, m), 8.18 (1H, d, J=8.8 Hz),  
 8.25-8.32 (3H, m), 8.50 (1H, br s).

5 MS (FAB) m/z: 538 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 540 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>5</sub>S·0.4H<sub>2</sub>O

Calculated: C, 59.48; H, 4.58; Cl, 6.50; N, 7.71; S, 5.88.

Found: C, 59.60; H, 4.56; Cl, 6.50; N, 7.52; S, 5.92.

[Example A-155] 1-[4-(2-Aminomethylpyridin-4-yl)benzoyl]-  
 10 4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
 hydrochloride

At room temperature, 1-[4-(2-azidomethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
 (159 mg) was dissolved in tetrahydrofuran (5 ml), followed  
 15 by the addition of water (0.5 ml) and triphenylphosphine  
 (114 mg). The resulting mixture was stirred for 18 hours.  
 The residue obtained by distilling off the solvent under  
 reduced pressure was purified by chromatography on a silica  
 gel column (10% methanol - dichloromethane), followed by  
 20 dissolution in dichloromethane. To the resulting solution,  
 1N hydrochloric acid in ethanol and water were added. The  
 resulting mixture was then concentrated. The crystals were  
 collected by filtration and washed with ethyl acetate,  
 whereby the title compound (53 mg, 30%) was obtained.

25 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.07 (4H, br), 3.30-4.20 (4H, m),  
 4.24 (1H, d, J=5.8 Hz), 4.27 (1H, d, J=5.8 Hz), 7.51 (2H, d, J=8.3 Hz),

7.71-7.78 (2H,m), 7.80-7.87 (3H,m), 7.89 (1H,br s),  
8.19 (1H,d,J=8.8Hz), 8.25-8.30 (2H,m), 8.42 (2H,br s),  
8.50 (1H,br s), 8.69 (1H,d,J=5.4Hz).  
MS (FAB) m/z: 521 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 523 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 Elementary analysis for C<sub>27</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>3</sub>S·1.5HCl·2.1H<sub>2</sub>O  
Calculated: C, 52.85; H, 5.04; Cl, 14.45; N, 9.13; S, 5.23.  
Found: C, 52.69; H, 4.93; Cl, 14.60; N, 9.21; S, 5.25.  
[Example A-156] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[4-[2-(dimethylaminomethyl)pyridin-4-yl]benzoyl]piperazine  
10 hydrochloride

In the same manner as in Referential Example 178, the  
corresponding bromo compound was obtained using 1-[(6-  
chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-  
hydroxymethylpyridin-4-yl)benzoyl]piperazine (300 mg). To  
15 the resulting compound, dimethylamine hydrochloride (469  
mg) and potassium carbonate (795 mg) were added, followed  
by stirring for 24 hours. The solvent was then distilled  
off under reduced pressure. Ethyl acetate and water were  
added to the residue to separate the organic layer. The  
20 organic layer thus obtained was dried over anhydrous sodium  
sulfate. The residue obtained by distilling off the  
solvent under reduced pressure was purified by  
chromatography on a silica gel column (3 to 5% methanol -  
dichloromethane). Hydrochloric acid in ethanol was added  
25 and the resulting mixture was concentrated. Ethyl acetate  
was added to the concentrate. The colorless powder thus



obtained was collected by filtration and dried, whereby the title compound (74 mg, 21%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.82 (6H, s), 3.07 (4H, br), 3.30-3.90 (4H, m), 4.50 (2H, br s), 7.51 (2H, d,  $J=7.8\text{Hz}$ ),  
 5 7.73 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.79-7.85 (2H, m),  
 7.86 (2H, d,  $J=7.8\text{Hz}$ ), 8.00 (1H, br s), 8.19 (1H, d,  $J=8.8\text{Hz}$ ),  
 8.25-8.30 (2H, m), 8.50 (1H, br s), 8.73 (1H, d,  $J=4.9\text{Hz}$ ).  
 MS (FAB)  $m/z$ : 549  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 551  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{29}\text{H}_{29}\text{ClN}_4\text{O}_3\text{S} \cdot 1.1\text{HCl} \cdot 2\text{H}_2\text{O}$

10 Calculated: C, 55.71; H, 5.50; Cl, 11.91; N, 8.96; S, 5.13.  
 Found: C, 55.61; H, 5.49; Cl, 11.89; N, 9.18; S, 5.27.

[Example A-157] 1-[4-[2-[(tert-Butoxycarbonylamino)methyl]pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

15 In the same manner as in Referential Example 10, a reaction was effected, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47 (9H, s), 3.13 (4H, br), 3.40-4.00 (4H, m),  
 4.50 (2H, d,  $J=5.4\text{Hz}$ ), 5.57 (1H, br s), 7.35 (1H, dd,  $J=5.4, 1.5\text{Hz}$ ),  
 20 7.41 (2H, d,  $J=8.3\text{Hz}$ ), 7.44 (1H, br s), 7.57-7.65 (3H, m),  
 7.76 (1H, dd,  $J=8.3, 1.5\text{Hz}$ ), 7.90-7.97 (3H, m),  
 8.31 (1H, d,  $J=1.5\text{Hz}$ ), 8.59 (1H, d,  $J=5.4\text{Hz}$ ).  
 MS (FAB)  $m/z$ : 621  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 623  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-158]

25 2-[(tert-Butoxycarbonylamino)methyl]-4-[4-[4-[(6-

chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.42 (9H, s), 3.13 (4H, br), 3.40-4.00 (4H, m), 4.52 (2H, d,  $J=6.3\text{Hz}$ ), 5.86 (1H, br s), 7.39-7.44 (3H, m), 7.56-7.63 (4H, m), 7.77 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.91-7.97 (3H, m), 8.27 (1H, d,  $J=6.8\text{Hz}$ ), 8.31 (1H, d,  $J=2.0\text{Hz}$ ).

MS (FAB)  $m/z$ : 637  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 639  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 Elementary analysis for  $\text{C}_{32}\text{H}_{33}\text{ClN}_4\text{O}_6\text{S}\cdot 0.7\text{H}_2\text{O}$

Calculated: C, 59.15; H, 5.34; Cl, 5.46; N, 8.62; S, 4.94.

Found: C, 58.92; H, 5.41; Cl, 5.56; N, 8.52; S, 5.05.

[Example A-159]

15 2-Aminomethyl-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-7, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.07 (4H, br), 3.35-3.95 (4H, m), 4.24 (2H, d,  $J=5.4\text{Hz}$ ), 7.49 (2H, d,  $J=8.3\text{Hz}$ ), 7.73 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.80-7.87 (3H, m), 7.89 (1H, dd,  $J=6.8, 2.4\text{Hz}$ ), 8.17-8.22 (2H, m), 8.25-8.30 (2H, m), 8.45 (1H, d,  $J=6.8\text{Hz}$ ), 8.51 (1H, br s), 8.71 (3H, br s).

MS (FAB)  $m/z$ : 537  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 539  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{27}\text{H}_{25}\text{ClN}_4\text{O}_4\text{S}\cdot 1.7\text{HCl}\cdot \text{H}_2\text{O}$

25 Calculated: C, 52.56; H, 4.69; Cl, 15.51; N, 9.08; S, 5.20.

Found: C, 52.69; H, 4.85; Cl, 15.51; N, 8.90; S, 5.13.

[Example A-160] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-cyanopyridin-4-yl)benzoyl]piperazine

In dichloromethane (100 ml), 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide (1.67 g) was dissolved, followed by the addition of trimethylsilylcyanide (0.42 ml) and dimethylcarbamoyl chloride (0.30 ml). The resulting mixture was stirred at room temperature for 24 hours. An aqueous solution of sodium bicarbonate and dichloromethane were added to the reaction mixture to separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (1% methanol - dichloromethane), whereby the title compound (1.44 g, 84%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.14 (4H, br s), 3.49 (2H, br s), 3.89 (2H, br s), 7.47 (2H, d,  $J=8.3\text{Hz}$ ), 7.55-7.72 (4H, m), 7.76 (1H, dd,  $J=8.8, 1.5\text{Hz}$ ), 7.87 (1H, s), 7.90-8.04 (3H, m), 8.31 (1H, br s), 8.77 (1H, d,  $J=4.9\text{Hz}$ ).

MS (FAB)  $m/z$ : 517  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 519  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{27}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S} \cdot 0.05\text{CH}_2\text{Cl}_2$

Calculated: C, 62.33; H, 4.08; Cl, 7.48; N, 10.75; S, 6.15.

Found: C, 62.16; H, 4.20; Cl, 7.65; N, 10.69; S, 6.04.

[Example A-161] 4-[4-[[4-[(6-Chloronaphthalen-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-cyanopyridine  
N-oxide

In the same manner as in Example A-6, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.13(4H, br s), 3.60(2H, br s), 3.87(2H, br s), 7.46(2H, d,  $J=8.3\text{Hz}$ ), 7.54-7.65(4H, m), 7.76(1H, dd,  $J=8.3, 1.5\text{Hz}$ ), 7.83(1H, d,  $J=2.9\text{Hz}$ ), 7.90-7.97(3H, m), 8.28-8.33(2H, m).

MS (FAB)  $m/z$ : 533  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 535  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 Elementary analysis for  $\text{C}_{27}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}$

Calculated: C, 60.84; H, 3.97; Cl, 6.65; N, 10.51; S, 6.02.

Found: C, 60.76; H, 4.04; Cl, 6.64; N, 10.39; S, 6.05.

[Example A-162] 1-[4-[2-[2-(tert-butoxycarbonylamino)ethyl]pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In a similar manner to Example A-3 and Example A-4, a reaction was effected using methyl 4-[2-[2-(tert-butoxycarbonylamino)ethyl]pyridin-4-yl]benzoate as a starting material, whereby the title compound was obtained.

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.42(9H, s), 3.04(2H, t,  $J=6.4\text{Hz}$ ), 3.12(4H, br), 3.45-4.00(6H, m), 5.11(1H, br s), 7.31(1H, dd,  $J=5.4, 2.0\text{Hz}$ ), 7.35(1H, br s), 7.41(2H, d,  $J=8.3\text{Hz}$ ), 7.58-7.65(3H, m), 7.77(1H, dd,  $J=8.3, 1.5\text{Hz}$ ), 7.90-7.97(3H, m), 8.31(1H, s), 8.59(1H, d,  $J=5.4\text{Hz}$ ).

25 MS (FAB)  $m/z$ : 635  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 637  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $C_{33}H_{35}ClN_4O_5S$

Calculated: C, 62.40; H, 5.55; N, 8.82.

Found: C, 62.78; H, 5.93; N, 8.51.

[Example A-163] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-[2-(tert-butoxycarbonylamino)ethyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.39(9H,s), 3.00-3.30(6H,m), 3.50-4.00(6H,m), 5.28(1H,br s), 7.37(1H,dd,J=6.8,2.9Hz), 7.41(2H,d,J=8.3Hz), 7.51(1H,br s), 7.56-7.63(3H,m), 7.77(1H,dd,J=8.3,1.5Hz), 7.91-7.97(3H,m), 8.28(1H,d,J=6.8Hz), 8.31(1H,d,J=1.5Hz).

MS (FAB)  $m/z$ : 651  $[(M+H)^+, Cl^{35}]$ , 653  $[(M+H)^+, Cl^{37}]$ .

15 Elementary analysis for  $C_{33}H_{35}ClN_4O_6S \cdot 0.8H_2O$

Calculated: C, 59.55; H, 5.54; N, 8.42.

Found: C, 59.75; H, 5.61; N, 8.07.

[Example A-164] 2-(2-Aminoethyl)-4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

20 In the same manner as in Example A-7, the title compound was obtained using 4-[4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-[2-(tert-butoxycarbonylamino)ethyl]pyridine N-oxide as a starting material.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.95-3.30 (6H,m), 3.30-3.90 (6H,m),  
 7.47 (2H,d,J=8.3Hz), 7.71-8.10 (8H,m), 8.19 (1H,d,J=8.8Hz),  
 8.26-8.30 (2H,m), 8.37 (1H,d,J=6.8Hz), 8.51 (1H,br s).  
 MS (FAB)  $m/z$ : 551 [(M+H) $^+$ , Cl $^{35}$ ], 553 [(M+H) $^+$ , Cl $^{37}$ ].

5 Elementary analysis for  $\text{C}_{28}\text{H}_{27}\text{ClN}_4\text{O}_4\text{S}\cdot 1.1\text{HCl}\cdot 1.6\text{H}_2\text{O}$

Calculated: C, 54.24; H, 5.09; Cl, 12.01; N, 9.04; S, 5.17.

Found: C, 54.40; H, 5.36; Cl, 11.90; N, 8.97; S, 5.27.

[Example A-165] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-5-methoxycarbonyl-1-[4-(pyridin-4-yl)benzoyl]-1,2,3,4-tetrahydropyrazine

10 In N,N-dimethylformamide (1 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (60 mg) and p-nitrophenyl 4-(pyridin-4-yl)benzoate (52 mg) were dissolved, followed by the  
 15 addition of sodium hydride (60% in oil, 7.20 mg) under ice cooling. The resulting mixture was stirred for 1 hour. Water and ethyl acetate were added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate and the solvent was  
 20 concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 2:1), followed by dissolution in ethanol. To the resulting solution, 1N aqueous hydrochloric acid in ethanol was added and the resulting  
 25 mixture was concentrated, whereby the title compound (58 mg, 60%) was obtained as pale yellow powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.51 (2H, s), 3.79 (3H, s), 3.99 (2H, s),  
 7.60 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.68 (1H, br), 7.76 (2H, d,  $J=7.8\text{Hz}$ ),  
 7.90 (2H, d,  $J=7.8\text{Hz}$ ), 7.92-7.99 (3H, m), 8.12 (2H, d,  $J=5.4\text{Hz}$ ),  
 8.16 (1H, dd,  $J=8.8, 1.5\text{Hz}$ ), 8.58 (1H, br s), 8.93 (2H, d,  $J=5.4\text{Hz}$ ).

5 MS (FAB)  $m/z$ : 548  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 550  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{28}\text{H}_{22}\text{ClN}_3\text{O}_5\text{S}\cdot 0.8\text{HCl}\cdot 1.3\text{H}_2\text{O}$

Calculated: C, 55.99; H, 4.26; Cl, 10.63; N, 7.00; S, 5.34.

Found: C, 55.96; H, 4.31; Cl, 10.43; N, 6.94; S, 5.56.

[Example A-166] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-5-  
 10 methoxycarbonyl-4-[4-(pyridin-4-yl)benzoyl]-1,2,3,4-  
 tetrahydropyrazine

In the same manner as in Referential Example 7, the  
 title compound was obtained using 4-(4-bromobenzoyl)-1-[(6-  
 chloronaphthalen-2-yl)sulfonyl]-5-methoxycarbonyl-1,2,3,4-  
 15 tetrahydropyrazine as a starting material.

$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ : 3.10-3.90 (7H, m), 7.43 (1H, s),  
 7.66 (2H, d,  $J=8.3\text{Hz}$ ), 7.78 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
 7.96 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.02 (2H, d,  $J=8.3\text{Hz}$ ), 8.20-  
 8.38 (5H, m), 8.74 (1H, br s), 8.94 (2H, d,  $J=6.3\text{Hz}$ ).

20 MS (FAB)  $m/z$ : 548  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 550  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{28}\text{H}_{22}\text{ClN}_3\text{O}_5\text{S}\cdot 0.8\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 57.37; H, 4.09; Cl, 10.89; N, 7.17; S, 5.47.

Found: C, 57.24; H, 4.15; Cl, 10.88; N, 6.97; S, 5.29.

[Example A-167] cis-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-  
 25 4-[4-(2-cyanopyridin-4-yl)benzoyl]-2,6-dimethylpiperazine

In the same manner as in Example A-160, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.40-1.60 (6H,m), 2.40-2.60 (2H,m), 3.40-3.90 (3H,m), 4.40-4.90 (1H,br), 7.43 (2H,d,J=8.3Hz),  
 5 7.60 (1H,dd,J=8.8,2.0Hz), 7.64 (2H,d,J=8.3Hz),  
 7.69 (1H,dd,J=5.4,2.0Hz), 7.76 (1H,dd,J=8.8,1.5Hz),  
 7.88 (1H,d,J=2.0Hz), 7.90-7.95 (3H,m), 8.31 (1H,d,J=1.5Hz),  
 8.78 (1H,d,J=5.4Hz).

MS (FAB) m/z: 545 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 547 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 Elementary analysis for C<sub>29</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>3</sub>S

Calculated: C, 63.90; H, 4.62; Cl, 6.50; N, 10.28; S, 5.88.

Found: C, 63.87; H, 4.98; Cl, 6.33; N, 9.96; S, 5.75.

[Example A-168] 4-[4-[[cis-4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,6-dimethylpiperazin-1-yl]carbonyl]phenyl]-2-  
 15 cyanopyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.42-1.55 (6H,m), 2.43-2.60 (2H,m), 3.40-3.90 (3H,m), 4.40-4.90 (1H,br), 7.42 (2H,d,J=8.3Hz),  
 20 7.58 (2H,d,J=8.3Hz), 7.60-7.65 (2H,m),  
 7.76 (1H,dd,J=8.8,2.0Hz), 7.83 (1H,d,J=2.9Hz), 7.90-7.95 (3H,m), 8.29-8.32 (2H,m).

MS (FAB) m/z: 561 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 563 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>29</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>4</sub>S·0.3H<sub>2</sub>O

25 Calculated: C, 61.49; H, 4.56; Cl, 6.26; N, 9.89; S, 5.66.



Found: C, 61.47; H, 4.63; Cl, 6.13; N, 9.72; S, 5.73.

[Example A-169] 1-[4-[(3-Aminomethyl)phenyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example A-4 and Example A-7,  
5 a reaction was effected, whereby the title compound was  
obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.07(4H,br), 3.51(2H,br), 3.69(2H,br),  
4.09(2H,s), 7.45(2H,d,J=8.3Hz), 7.47-7.55(2H,m), 7.66-  
7.76(4H,m), 7.80-7.87(2H,m), 8.19(2H,d,J=8.8Hz), 8.25-  
10 8.42(4H,m), 8.51(1H,br s).

MS (FAB) m/z: 520 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 522 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>28</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl

Calculated: C, 60.34; H, 4.89; Cl, 12.74; N, 7.55; S, 5.76.

Found: C, 60.15; H, 4.89; Cl, 12.44; N, 7.52; S, 5.80.

15 [Example A-170] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[[2,5-dihydro-5-oxo-3-(pyridin-4-yl)-1,2,4-triazin-6-  
yl]carbonyl]piperazine

In the same manner as in Example A-4, the title  
compound was obtained.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.94(2H,br s), 3.07(2H,br s),  
3.52(2H,br s), 3.73(2H,br s), 7.74(1H,dd,J=8.8,2.4Hz),  
7.84(1H,dd,J=8.8,2.0Hz), 7.99(2H,d,J=6.3Hz),  
8.20(1H,d,J=8.8Hz), 8.26-8.31(2H,m), 8.53(1H,br s),  
8.87(2H,d,J=6.3Hz).

25 MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{23}H_{19}ClN_6O_4S \cdot 0.6HCl \cdot 1.5H_2O$

Calculated: C, 49.34; H, 4.07; Cl, 10.13; N, 15.01; S, 5.73.

Found: C, 49.25; H, 4.01; Cl, 10.12; N, 15.07; S, 5.59.

[Example A-171] trans-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-105, the title compound was obtained as colorless amorphous powder by using trans-2,6-bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.50-2.65 (2H, m), 3.70-3.80 (2H, m), 3.30-3.40 (4H, m), 3.46 (6H, s), 4.23 (2H, br), 7.60 (2H, d,  $J=8.3$  Hz), 7.74 (1H, d,  $J=8.8$  Hz), 7.85 (1H, d,  $J=8.3$  Hz), 8.03 (2H, d,  $J=8.3$  Hz), 8.15-8.40 (4H, m), 8.53 (1H, s), 8.90-9.00 (2H, m).

MS (FAB)  $m/z$ : 636  $[(M+H)^+, Cl^{35}]$ , 638  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{32}H_{30}ClN_3O_7S \cdot HCl \cdot 2.6H_2O$

Calculated: C, 53.42; H, 5.07; Cl, 9.86; N, 5.84; S, 4.46.

Found: C, 53.21; H, 4.75; Cl, 9.91; N, 5.80; S, 4.54.

[Example A-172] cis-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-171, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.70-3.00 (6H,m), 3.40-3.80 (2H,m),  
 3.51 (3H,s), 3.68 (3H,s), 4.13 (1H,br), 4.97 (1H,br),  
 7.58 (2H,d,J=7.8Hz), 7.70-7.75 (1H,m), 7.80-7.90 (1H,m),  
 8.03 (2H,d,J=8.3Hz), 8.19 (1H,d,J=8.8Hz), 8.25-8.35 (4H,m),  
 8.55 (1H,s), 8.90-8.95 (2H,m).

MS (FAB) m/z: 636 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 638 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>32</sub>H<sub>30</sub>ClN<sub>3</sub>O<sub>7</sub>S·HCl·0.3H<sub>2</sub>O

Calculated: C, 56.69; H, 4.70; Cl, 10.46; N, 6.20; S, 4.73.

Found: C, 56.72; H, 4.66; Cl, 10.31; N, 6.03; S, 4.71.

[Example A-173] cis-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-35, the title compound was obtained using cis-2,6-

bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.30-2.60 (10H,m), 2.80-2.90 (2H,m),  
 3.45-3.55 (1H,m), 3.75-3.85 (1H,m), 4.10-4.20 (1H,m), 4.95-  
 5.05 (1H,m), 6.85 (1H,br s), 7.03 (1H,br s), 7.40 (1H,br s),  
 7.45 (1H,br s), 7.56 (2H,d,J=8.3Hz), 7.70-7.75 (1H,m), 7.80-  
 7.85 (1H,m), 8.02 (2H,d,J=8.3Hz), 8.18 (1H,d,J=8.8Hz), 8.25-  
 8.40 (4H,m), 8.52 (1H,s), 8.95 (2H,d,J=6.8Hz).

MS (FAB) m/z: 606 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 608 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>30</sub>H<sub>28</sub>ClN<sub>5</sub>O<sub>5</sub>S·1.2HCl·2.8H<sub>2</sub>O

Calculated: C, 51.45; H, 5.01; N, 11.14; Cl, 10.00; S, 4.58.

Found: C, 51.52; H, 5.30; N, 11.33; Cl, 10.01; S, 4.72.

5 [Example A-174] 4-[4-[[cis-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

10  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.30-2.60 (4H,m), 2.75-2.90 (2H,m), 3.45-3.55 (1H,m), 3.75-3.85 (1H,m), 4.10-4.20 (1H,m), 4.90-5.00 (1H,m), 6.86 (1H,br), 7.02 (1H,br), 7.30-7.50 (4H,m), 7.70-7.85 (6H,m), 8.18 (1H,d,  $J=8.8\text{Hz}$ ), 8.25-8.35 (4H,m), 8.52 (1H,s).

15 MS (FAB)  $m/z$ : 622  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 624  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{30}\text{H}_{28}\text{ClN}_5\text{O}_6\text{S}\cdot 1.6\text{H}_2\text{O}$

Calculated: C, 55.36; H, 4.83; Cl, 5.45; N, 10.76; S, 4.93.

Found: C, 55.05; H, 4.77; Cl, 5.77; N, 10.51; S, 4.90.

20 [Example A-175] 4-[4-[[cis-2,6-Bis(ethoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.85-2.95 (4H,m), 3.20-3.40 (4H,m), 3.63 (6H,s), 4.25-4.35 (2H,m), 7.45-7.50 (4H,m), 7.55-

7.65 (3H,m), 7.70-7.80 (1H,m), 7.90-7.95 (3H,m), 8.25-8.35 (3H,m).

MS (FAB) m/z: 652 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 654 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>32</sub>H<sub>30</sub>ClN<sub>3</sub>O<sub>8</sub>S·2.3H<sub>2</sub>O

5 Calculated: C, 55.42; H, 5.03; Cl, 5.11; N, 6.06; S, 4.62.

Found: C, 55.50; H, 4.93; Cl, 5.12; N, 5.89; S, 4.54.

[Example A-176] trans-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

10 In the same manner as in Example A-105, the title compound was obtained using trans-2,6-bis(carbamoylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.50-2.60 (4H,m), 3.20-3.30 (4H,m), 4.15-4.25 (2H,m), 6.87 (2H,br s), 7.40 (2H,br s), 7.62 (2H,d,J=8.8Hz), 7.72 (1H,d,J=8.3Hz), 7.82 (1H,d,J=8.8Hz), 8.02 (2H,d,J=8.3Hz), 8.16 (1H,d,J=8.8Hz), 8.20-8.40 (4H,m), 8.51 (1H,s), 8.90-9.00 (2H,m).

MS (FAB) m/z: 606 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 608 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 Elementary analysis for C<sub>30</sub>H<sub>28</sub>ClN<sub>5</sub>O<sub>5</sub>S·1.2HCl·3H<sub>2</sub>O

Calculated: C, 51.19; H, 5.04; Cl, 11.08; N, 9.95; S, 4.56.

Found: C, 51.10; H, 4.97; Cl, 11.17; N, 9.71; S, 4.64.

[Example A-177] 4-[4-[[trans-2,6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

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In the same manner as in Example A-6, the title

compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.55-2.65 (2H,m), 2.65-2.80 (2H,m), 3.20-3.60 (4H,m), 4.25-4.35 (2H,m), 4.90-5.00 (1H,m), 6.98 (2H,br), 7.48 (2H,br), 7.55-7.65 (2H,m), 7.80-8.00 (6H,m), 8.20-8.40 (5H,m), 8.60 (1H,s).

MS (FAB)  $m/z$ : 622  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 624  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-178] *trans*-2,6-bis(carboxymethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

10 In the same manner as in Example A-3, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.50-2.75 (4H,m), 3.25-3.45 (4H,m), 4.15-4.25 (2H,m), 7.52 (2H,d,  $J=8.3\text{Hz}$ ), 7.70-7.75 (3H,m), 7.80-7.85 (3H,m), 8.16 (1H,d,  $J=8.8\text{Hz}$ ), 8.20-8.30 (2H,m), 8.51 (1H,s), 8.60-8.70 (2H,m), 12.32 (2H,s).

MS (FAB)  $m/z$ : 608  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 610  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{30}\text{H}_{26}\text{ClN}_3\text{O}_7\text{S}\cdot 0.2\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 57.71; H, 4.39; Cl, 6.81; N, 6.73; S, 5.14.

Found: C, 57.78; H, 4.35; Cl, 6.73; N, 6.68; S, 5.11.

20 [Example A-179] *trans*-2,6-Bis(2-hydroxyethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine

In tetrahydrofuran (40 ml), *trans*-2,6-bis(carboxymethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[4-(pyridin-4-yl)benzoyl]piperazine (269 mg) was suspended,

25

followed by the addition of N,N-diisopropylethylamine (480  
µl) and 1-benzotriazolyloxy-tris(pyrrolidino)phosphonium  
hexafluorophosphate (672 mg) under ice cooling. The  
resulting mixture was stirred for 3.5 hours at room  
5 temperature. Under ice cooling, sodium borohydride (297  
mg) was added and the resulting mixture was stirred for 15  
hours at room temperature. The reaction mixture was ice  
cooled and added with water and ethyl acetate to separate  
the organic layer. The organic layer thus obtained was  
10 washed with aqueous NaCl solution, dried over anhydrous  
sodium sulfate. The residue obtained by distilling off the  
solvent under reduced pressure was purified by  
chromatography on a silica gel column (4% methanol -  
dichloromethane), followed by dissolution in  
15 tetrahydrofuran. Saturated hydrochloride in methanol was  
added to the resulting solution and the resulting mixture  
was concentrated to dryness. Ethyl acetate was then added  
to the residue to crystallize the same, whereby the title  
compound was obtained.

20  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.60-1.80 (2H,m), 1.80-1.95 (2H,m), 3.20-  
3.40 (6H,m), 3.95-4.05 (2H,m), 7.59 (2H,d,J=8.3Hz), 7.70-  
7.75 (3H,m), 7.80-7.90 (31H,m), 7.99 (2H,d,J=8.3Hz),  
8.17 (1H,d,J=8.8Hz), 8.20-8.30 (4H,m), 8.54 (1H,s), 8.85-  
8.95 (2H,m).

25 HRMS (FAB)  $m/z$ : 580.1633 ( $\text{M}+\text{H}$ ) $^+$  (calcd for  $\text{C}_{30}\text{H}_{30}\text{ClN}_3\text{O}_5\text{S}$   
580.1673).

[Example A-180] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-4, the title compound was obtained.

5  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.74 (3H, s), 2.99-3.81 (8H, br),  
7.71 (1H, s), 7.33 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.51 (1H, d,  $J=8.8\text{Hz}$ ),  
7.58 (2H, d,  $J=8.3\text{Hz}$ ), 7.79 (1H, d,  $J=2.0\text{Hz}$ ), 8.00 (2H, d,  $J=8.3\text{Hz}$ ),  
8.77-8.84 (1H, m), 8.79 (1H, d,  $J=6.3\text{Hz}$ ), 12.50 (1H, s).  
MS (FAB)  $m/z$ : 495  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 497  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 Elementary analysis for  $\text{C}_{25}\text{H}_{23}\text{ClN}_4\text{O}_3\text{S}\cdot 0.9\text{HCl}\cdot \text{H}_2\text{O}$   
Calculated: C, 55.01; H, 4.78; Cl, 12.34; N, 10.26; S,  
5.87.  
Found: C, 54.99; H, 5.01; Cl, 12.12; N, 10.03; S,  
5.88.

15 [Example A-181] 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

20 MS (FAB)  $m/z$ : 511  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 513  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .  
 $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.95-3.18 (4H, br), 3.37-3.81 (4H, br),  
7.03 (1H, s), 7.34 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.47 (2H, d,  $J=8.3\text{Hz}$ ),  
7.51 (1H, d,  $J=8.8\text{Hz}$ ), 7.66 (1H, dd,  $J=6.8, 2.9\text{Hz}$ ), 7.79 (1H, s),  
7.80 (2H, d,  $J=8.3\text{Hz}$ ), 7.91 (1H, d,  $J=2.9\text{Hz}$ ), 8.30 (1H, d,  $J=6.8\text{Hz}$ ),  
25 12.42 (1H, s).



Elementary analysis for  $C_{25}H_{23}ClN_4O_4S \cdot 0.8H_2O$

Calculated: C, 57.15; H, 4.72; Cl, 6.75; N, 10.66; S, 6.10.

Found: C, 57.22; H, 4.64; Cl, 7.04; N, 10.42; S, 6.17.

[Example A-182] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-  
5 (pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

At room temperature, 1-[(5-bromopyrimidin-2-  
yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine  
(500 mg) and (pyridin-2-yl)tributyltin (418 mg) were  
dissolved in N,N-dimethylformamide (10 ml). To the  
10 reaction mixture was added  
tetrakis(triphenylphosphine)palladium(0) (69 mg), followed  
by stirring at 100°C for 9 hours. After cooling to room  
temperature, ethyl acetate and ammonia solution were added.  
The resulting mixture was separated by ethyl acetate and  
15 water. The organic layer was dried over anhydrous sodium  
sulfate. The filtrate was concentrated and the residue was  
purified by chromatography on a silica gel column (4%  
methanol - methylene chloride). The resulting fraction was  
added with ethanol, followed by concentration. Diethyl  
20 ether was then added to the concentrate. Colorless powder  
thus precipitated was collected by filtration and dried,  
whereby the free form (254 mg) of the title compound was  
obtained. The resulting free form was dissolved in  
methylene chloride, followed by the addition of 1N  
25 hydrochloric acid (in ethanol) to make the solution acidic.  
After concentration, ethyl acetate and diethyl ether were

added, followed by concentration. Colorless powder thus precipitated was collected by filtration and dried, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-2.98 (2H,m), 3.10-3.15 (2H,m), 3.30-3.41 (2H,m), 3.75-3.85 (2H,m), 7.05 (1H,d,J=2.0Hz), 7.35 (1H,dd,J=2.0 and 8.8Hz), 7.47-7.53 (2H,m), 7.80 (1H,d,J=2.0Hz), 8.00 (1H,dt,J=2.0 and 8.3Hz), 8.17 (1H,d,J=8.3Hz), 8.76 (1H,d,J=4.4Hz), 9.47 (2H,s), 12.47 (1H,s).

MS (FAB) m/z: 483 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 485 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-183] 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.10-3.20 (2H,m), 3.20-3.30 (2H,m), 3.50-3.60 (2H,m), 3.85-3.95 (2H,m), 6.97 (1H,s), 7.30-7.52 (5H,m), 7.68 (1H,s), 8.39 (1H,d,J=5.9Hz), 9.28 (2H,s), 9.50 (1H,s).

MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-184] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.01-3.10 (2H,m), 3.17-3.26 (2H,m), 3.39-3.47 (2H,m), 3.79-3.87 (2H,m), 7.52 (1H,dd,J=7.3 and 4.9Hz),

7.61 (1H, d, J=8.8Hz), 8.01 (1H, dt, J=1.5 and 7.3Hz),  
 8.10 (1H, d, J=8.8Hz), 8.12 (1H, s), 8.18 (1H, d, J=7.3Hz),  
 8.35 (1H, s), 8.76 (1H, d, J=4.9Hz), 9.48 (2H, s).  
 MS (FAB) m/z: 500 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 502 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example A-185] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.24 (2H, t, J=4.9Hz), 3.33 (2H, t, J=4.9Hz),  
 3.63 (2H, t, J=4.9Hz), 3.99 (2H, t, J=4.9Hz), 7.36-7.53 (4H, m),  
 7.78 (1H, s), 7.84 (1H, d, J=8.3Hz), 7.88 (1H, br s), 8.36-  
 8.39 (1H, m), 9.29 (2H, s).

MS (FAB) m/z: 516 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 518 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

15 [Example A-186] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.71 (3H, s), 2.96 (2H, br s), 3.16 (2H, br  
 s), 3.30 (2H, br s), 3.81 (2H, br s), 7.05 (1H, s),  
 7.35 (1H, d, J=8.8Hz), 7.51 (1H, d, J=8.8Hz), 7.81 (1H, s),  
 8.13 (1H, br s), 8.23 (1H, br s), 8.84 (1H, br s), 9.40 (2H, s),  
 12.50 (1H, s).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

25 [Example A-187] 4-[2-[[4-[(5-Chloroindol-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.77(3H,s), 3.16-3.20(2H,m), 3.28-3.31(2H,m), 3.57-3.60(2H,m), 3.95-3.98(2H,m), 6.97(1H,d,J=1.5Hz), 7.32-7.42(3H,m), 7.50(1H,d,J=2.9Hz), 7.69(1H,s), 8.39(1H,d,J=6.8Hz), 8.92-9.05(3H,m).

MS (FAB)  $m/z$ : 513  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 515  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 [Example A-188] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

15  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.74(3H,s), 3.01-3.09(2H,m), 3.17-3.25(2H,m), 3.38-3.45(2H,m), 3.80-3.90(2H,m), 7.61(1H,dd,J=8.8,2.0Hz), 8.10(1H,d,J=8.8Hz), 8.13(1H,s), 8.20(1H,d,J=5.9Hz), 8.31(1H,br s), 8.36(1H,d,J=2.0Hz), 8.87(1H,d,J=5.9Hz), 9.43(2H,s).

20 MS (FAB)  $m/z$ : 514  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 516  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-189] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

25

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.60 (3H, s), 3.24 (2H, br), 3.34 (2H, br),  
 3.60 (2H, br), 3.99 (2H, br), 7.39 (1H, dd, J=2.4 and 6.8 Hz),  
 7.47 (1H, dd, J=1.5 and 8.8 Hz), 7.50 (1H, d, J=2.4 Hz),  
 7.78 (1H, s), 7.83 (1H, d, J=8.8 Hz), 7.88 (1H, d, J=1.5 Hz),  
 8.38 (1H, d, J=6.8 Hz), 8.99 (2H, s).

MS (FAB) m/z: 530 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 532 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-190] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
 4-[[5-(3-fluoropyridin-4-yl)pyrimidin-2-  
 yl]carbonyl]piperazine

10 In the same manner as in Example A-182, the title  
 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.06 (2H, br s), 3.21 (2H, br s),  
 3.44 (2H, br s), 3.84 (2H, br s), 7.60 (1H, dd, J=8.8, 2.0 Hz),  
 7.84 (1H, dd, J=6.4, 4.9 Hz), 8.09 (1H, d, J=8.8 Hz), 8.12 (1H, s),  
 8.35 (1H, d, J=2.0 Hz), 8.62 (1H, d, J=4.9 Hz), 8.79 (1H, d, J=2.0 Hz),  
 9.20 (2H, s).

MS (FAB) m/z: 518 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 520 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-191] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-  
 yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-3-  
 20 fluoropyridine N-oxide

In the same manner as in Example A-6, the title  
 compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.23-3.27 (2H, m), 3.32-3.36 (2H, m), 3.59-  
 3.63 (2H, m), 3.98-4.01 (2H, m), 7.36-7.43 (1H, m),  
 7.47 (1H, d, J=8.3 Hz), 7.78 (1H, s), 7.83 (1H, d, J=8.3 Hz),

7.88 (1H, s), 8.18 (1H, d, J=6.8 Hz), 8.30 (1H, d, J=5.9 Hz),  
9.00 (2H, s).

HRMS (FAB) m/z: 534.0468 [(M+H)<sup>+</sup> calcd for C<sub>22</sub>H<sub>18</sub>ClFN<sub>5</sub>O<sub>4</sub>S<sub>2</sub>,  
534.0473].

5 [Example A-192]

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2,6-  
dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title  
compound was obtained.

10 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.71 (6H, s), 2.95 (2H, br s), 3.16 (2H, br  
s), 3.37 (2H, br s), 3.81 (2H, br s), 7.05 (1H, s),  
7.35 (1H, dd, J=8.8, 2.0 Hz), 7.51 (1H, d, J=8.8 Hz), 7.80 (1H, br s),  
8.14 (2H, br s), 9.39 (2H, s), 12.50 (1H, s).  
MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

15 [Example A-193] 4-[2-[[4-[(5-Chloroindol-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,6-  
dimethylpyridine N-oxide

In the same manner as in Example A-6, the title  
compound was obtained.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.61 (6H, s), 3.18 (2H, d, J=4.9 Hz),  
3.29 (2H, d, J=4.9 Hz), 3.59 (2H, d, J=4.9 Hz), 3.97 (2H, d, J=4.9 Hz),  
6.97 (1H, d, J=1.5 Hz), 7.35 (1H, dd, J=8.8 and 2.0 Hz), 7.38-  
7.43 (3H, m), 7.69 (1H, d, J=2.0 Hz), 8.89 (1H, br s), 8.98 (2H, s).  
MS (FAB) m/z: 527 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 529 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

25 [Example A-194] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-

(2,5-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.39(3H,s), 2.68(3H,s), 2.97(2H,br s), 3.16(2H,br s), 3.40(2H,br s), 3.81(2H,br s), 7.06(1H,s), 7.34(1H,dd,J=8.8 and 2.0Hz), 7.52(1H,d,J=8.8Hz), 7.79-7.83(2H,m), 8.76(1H,s), 9.32(2H,s), 12.52(1H,s).

MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 [Example A-195] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,5-dimethylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.25(3H,s), 2.54(3H,s), 3.15-3.25(2H,m), 3.25-3.38(2H,m), 3.55-3.65(2H,m), 3.90-4.05(2H,m), 6.97(1H,s), 7.13(1H,s), 7.34(1H,dd,J=8.8 and 1.5Hz), 7.41(1H,d,J=8.8Hz), 7.68(1H,d,J=1.5Hz), 8.28(1H,s), 8.78(2H,s), 9.20(1H,s).

20 MS (FAB) m/z: 527 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 529 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-196] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2,3-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

25 In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.33(3H,s), 2.76(3H,s), 2.97(2H,br s),  
3.17(2H,br s), 3.43(2H,br s), 3.82(2H,br s), 7.06(1H,s),  
7.34(1H,dd,J=8.8 and 2.0Hz), 7.52(1H,d,J=8.8Hz), 7.78-  
7.85(2H,m), 8.72(1H,d,J=5.9Hz), 9.01(2H,s), 12.52(1H,s).

5 MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-197] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,3-dimethylpyridine N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.27(3H,s), 2.61(3H,s),  
3.20(2H,t,J=4.9Hz), 3.31(2H,t,J=4.9Hz), 3.62(2H,t,J=4.9Hz),  
3.98(2H,t,J=4.9Hz), 6.97(1H,d,J=1.5Hz), 7.00(1H,d,J=6.8Hz),  
7.35(1H,dd,J=8.8 and 2.0Hz), 7.40(1H,d,J=8.8Hz),  
15 7.68(1H,d,J=2.0Hz), 8.29(1H,d,J=6.8Hz), 8.75(2H,s),  
9.02(1H,s).

MS (FAB) m/z: 527 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 529 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-198] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl-4-  
[[5-(2,3-dimethylpyridin-4-yl)pyridimin-2-yl]carbonyl]piperazine  
20

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.31(3H,s), 2.73(3H,s), 3.05(2H,br s),  
3.21(2H,br s), 3.46(2H,br s), 3.84(2H,br s),  
25 7.59(1H,dd,J=8.5,2.0Hz), 7.78(1H,d,J=5.4Hz),



8.08 (1H, d, J=8.5Hz), 8.12 (1H, s), 8.34 (1H, d, J=2.0Hz),  
8.70 (1H, d, J=5.4Hz), 9.00 (2H, s).

MS (FAB) m/z: 528 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 530 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-199] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,3-dimethylpyridine N-oxide

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.28 (3H, s), 2.60 (3H, s),  
10 3.26 (2H, d, J=4.9Hz), 3.35 (2H, d, J=4.9Hz), 3.64 (2H, d, J=4.9Hz),  
4.00 (2H, d, J=4.9Hz), 7.01 (1H, d, J=6.6Hz), 7.47 (1H, dd, J=1.7  
and 8.8Hz), 7.78 (1H, s), 7.83 (1H, d, J=8.8Hz),  
7.88 (1H, d, J=1.7Hz), 8.28 (1H, d, J=6.6Hz), 8.76 (2H, s).

MS (FAB) m/z: 544 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 546 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

15 [Example A-200] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(3,5-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.16 (6H, s), 2.99 (2H, br s), 3.17 (2H, br  
s), 3.42 (2H, br s), 3.82 (2H, br s), 7.06 (1H, s),  
7.34 (1H, d, J=8.8Hz), 7.51 (1H, d, J=8.8Hz), 7.80 (1H, s),  
8.72 (2H, br s), 8.91 (2H, s), 12.50 (1H, s).

MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

25 [Example A-201] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(6-

methypyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.57(3H,s), 2.96(2H,br s), 3.15(2H,br  
5 s), 3.36(2H,br s), 3.80(2H,br s), 7.05(1H,d,J=2.0Hz),  
7.35(1H,dd,J=8.8,2.0Hz), 7.38(1H,d,J=7.3Hz),  
7.51(1H,d,J=8.8Hz), 7.81(1H,d,J=2.0Hz), 7.89(1H,t,J=7.3Hz),  
7.96(1H,d,J=7.3Hz), 9.44(2H,s), 12.49(1H,s).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 [Example A-202] 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-6-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.59(3H,s), 3.15(2H,d,J=4.9Hz),  
3.26(2H,d,J=4.9Hz), 3.56(2H,d,J=4.9Hz), 3.94(2H,d,J=4.9Hz),  
6.97(1H,s), 7.30-7.41(5H,m), 7.69(1H,s), 9.07(1H,s),  
9.25(2H,s).

MS (FAB) m/z: 513 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 515 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example A-203] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(3-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.41(3H,s), 2.97(2H,br s), 3.16(2H,br  
25 s), 3.40(2H,br s), 3.80(2H,br s), 7.05(1H,s),

7.33 (1H, dd, J=8.8, 2.0Hz), 7.50 (1H, d, J=8.8Hz),  
 7.79 (1H, d, J=2.0Hz), 7.84 (1H, d, J=5.4Hz), 8.79 (1H, d, J=5.4Hz),  
 8.85 (1H, s), 9.04 (2H, s), 12.49 (1H, s).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example A-204] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(5-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.37 (3H, s), 2.94-2.97 (2H, m), 3.13-  
 10 3.16 (2H, m), 3.35-3.39 (2H, m), 3.78-3.81 (2H, m),  
 7.05 (1H, d, J=2.0Hz), 7.34 (1H, dd, J=8.8, 2.0Hz),  
 7.51 (1H, d, J=8.8Hz), 7.78-7.83 (2H, m), 8.07 (1H, d, J=8.3Hz),  
 8.60 (1H, d, J=1.5Hz), 9.44 (2H, s), 12.47 (1H, s).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

15 [Example A-205] 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-5-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.40 (3H, s), 3.16-3.19 (2H, m), 3.26-  
 3.29 (2H, m), 3.58-3.61 (2H, m), 3.95-3.98 (2H, m), 6.98 (1H, s),  
 7.20-7.41 (4H, m), 7.70 (1H, s), 8.24 (1H, s), 9.04 (1H, s),  
 9.27 (2H, s).

MS (FAB) m/z: 513 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 515 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

25 HRMS (FAB) m/z: 513.1144 (M+H)<sup>+</sup> (calcd for C<sub>23</sub>H<sub>22</sub>ClN<sub>6</sub>O<sub>4</sub>S,

513.1112).

[Example A-206] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(3-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title  
5 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.41(3H,s), 2.98(2H,br s), 3.15(2H,br  
s), 3.40(2H,br s), 3.81(2H,br s), 7.05(1H,s),  
7.34(1H,dd,J=8.8,2.0Hz), 7.45(1H,dd,J=7.8,4.9Hz),  
7.51(1H,d,J=8.8Hz), 7.80(1H,s), 7.85(1H,d,J=7.8Hz),  
10 8.59(1H,d,J=4.9Hz), 9.09(2H,s), 12.49(1H,s).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-207] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]thiocarbonyl]piperazine

In a mixed solvent of dimethoxyethane (10 ml) and  
15 toluene (10 ml) was suspended 1-[(5-chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine (100 mg) at room temperature,  
followed by the addition of Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide,  
20 42 mg). The resulting mixture was heated under reflux for 2 days. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by chromatography on a silica gel column (3 → 5% methanol - methylene chloride). 1N hydrochloric acid (in ethanol) was  
25 added to make acidic the purified product. After concentration, ethyl acetate was added. Yellow powder so

precipitated was collected by filtration and dried, whereby the title compound (34 mg) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.00(3H, br s), 3.28(2H, br s), 3.59(2H, br s), 4.44(2H, br s), 7.06(1H, s), 7.34(1H, dd, J=9.0, 2.0Hz), 7.51(1H, d, J=9.0Hz), 7.80(1H, d, J=2.0Hz), 8.21(2H, d, J=6.1Hz), 8.90(2H, d, J=6.1Hz), 9.33(2H, s), 12.51(1H, s).

MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-208] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(hydroxyimino)[5-(pyridin-4-yl)pyrimidin-2-yl]methyl]piperazine

In ethanol (50 ml) was suspended 1-[(5-chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]thiocarbonyl]piperazine (243 mg) at room temperature, followed by the successive addition of hydroxylamine hydrochloride (338 mg), sodium acetate (399 mg) and mercury (II) chloride (132 mg). The resulting mixture was stirred at room temperature for 6 hours. The insoluble matter was filtered off through Celite filtration. The residue was purified by chromatography on a silica gel column (7% methanol - methylene chloride), whereby two fractions were obtained. They were concentrated, respectively, whereby a low-polarity compound (20 mg, colorless powder) and a high-polarity compound (20 mg, colorless powder) were obtained.

Low-polarity compound:

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.01(4H, br s), 3.09(4H, br s),

7.00 (1H, s), 7.25-7.35 (1H, m), 7.49 (1H, d, J=9.0 Hz), 7.78 (1H, br s), 7.89 (2H, d, J=6.1 Hz), 8.73 (2H, d, J=6.1 Hz), 9.30 (2H, s).

HRMS (FAB) m/z: 498.1115 (M+H)<sup>+</sup> (calcd for C<sub>22</sub>H<sub>21</sub>ClN<sub>7</sub>O<sub>3</sub>S, 498.1115).

5 High-polarity compound:

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.06 (4H, br s), 3.30-3.32 (4H, unclear because of the overlapping with that of water), 7.03 (1H, s), 7.33 (1H, d, J=8.8 Hz), 7.51 (1H, d, J=8.8 Hz), 7.80 (1H, br s), 7.87 (2H, d, J=6.1 Hz), 8.73 (2H, d, J=6.1 Hz), 9.24 (2H, s).

10 HRMS (FAB) m/z: 498.1110 (M+H)<sup>+</sup> (calcd for C<sub>22</sub>H<sub>21</sub>ClN<sub>7</sub>O<sub>3</sub>S, 498.1115).

[Example A-209] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(hydrazono)[5-(pyridin-4-yl)pyrimidin-2-yl]methyl]piperazine

15 In a mixed solvent of ethanol (100 ml) and methylene chloride (100 ml) was suspended 1-[(5-chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]thiocarbonyl]piperazine (499 mg) at room temperature, followed by the successive addition of hydrazine  
20 monohydrate (146 µg) and mercury (II) chloride (272 mg). The resulting mixture was stirred at room temperature for 4 hours. After the solvent was distilled off, the residue was purified by chromatography on a silica gel column (8% methanol - methylene chloride). Methylene chloride was  
25 added and the resulting mixture was concentrated. Yellow crystals thus precipitated were collected by filtration and

dried, whereby the title compound (100 mg) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.03(8H, br s), 6.77(2H, br s),  
7.04(1H, s), 7.34(1H, dd, J=8.8 and 2.0Hz),  
7.52(1H, d, J=8.8Hz), 7.81(1H, d, J=2.0Hz), 7.88(2H, d, J=6.3Hz),  
5 8.73(2H, d, J=6.3Hz), 9.35(2H, s), 12.45(1H, s).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-210] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
4-[4-(pyridin-4-yl)benzylidene]piperazine

10 In the same manner as in Referential Example 7, the  
title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.45-2.52(2H, m), 2.57-2.61(2H, m), 3.12-  
3.16(2H, m), 3.20-3.24(2H, m), 6.44(1H, s),  
7.37(2H, d, J=8.3Hz), 7.56(1H, dd, J=8.5, 2.0Hz),  
7.91(2H, d, J=8.3Hz), 8.05(1H, d, J=8.5Hz), 8.07(1H, s),  
15 8.16(2H, d, J=6.6Hz), 8.31(1H, s), 8.82(2H, d, J=6.6Hz).

HRMS (FAB) m/z: 481.0783 (M+H)<sup>+</sup> (calcd for C<sub>25</sub>H<sub>22</sub>ClN<sub>2</sub>O<sub>2</sub>S<sub>2</sub>,  
481.0811).

[Example A-211] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[[5-(2-methylpyridin-4-yl)pyrimidin-2-  
20 yl]carbonyl]piperazine

In the same manner as in Example A-182, the title  
compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.69(3H, s), 2.93(2H, br s), 3.13(2H, br  
s), 3.37(2H, br s), 3.80(2H, br s), 7.75(1H, dd, J=8.8 and  
25 2.0Hz), 7.84(1H, d, J=7.8Hz), 8.10(1H, br s), 8.18-8.23(2H, m),

8.26-8.32 (2H, m), 8.53 (1H, br s), 8.82 (1H, d, J=5.9 Hz),  
9.38 (2H, s).

MS (FAB) m/z: 508 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 510 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-212] 4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.60 (3H, s), 3.13-3.17 (2H, m), 3.25-  
3.28 (2H, m), 3.55-3.59 (2H, m), 3.94-3.98 (2H, m),  
7.37 (1H, dd, J=6.8 and 2.9 Hz), 7.49 (1H, d, J=2.9 Hz),  
7.60 (1H, dd, J=8.8 and 2.0 Hz), 7.76 (1H, dd, J=8.8 and 2.0 Hz),  
7.90-7.97 (3H, m), 8.31 (1H, d, J=2.0 Hz), 8.37 (1H, d, J=6.8 Hz),  
8.97 (2H, s).

MS (FAB) m/z: 524 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 526 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-213] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.93 (2H, br s), 3.12 (2H, br s),  
3.36 (2H, br s), 3.81 (2H, br s), 7.50 (1H, dd, J=7.3 and 4.9 Hz),  
7.74 (1H, dd, J=8.8 and 2.0 Hz), 7.83 (1H, dd, J=8.8 and 1.5 Hz),  
7.96-8.03 (1H, m), 8.16 (1H, d, J=8.3 Hz), 8.19 (1H, d, J=8.8 Hz),  
8.25-8.31 (2H, m), 8.52 (1H, br s), 8.75 (1H, d, J=4.9 Hz),  
9.46 (2H, s).



MS (FAB) m/z: 494 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 496 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-214] 2-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

5 In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.13-3.16(2H,m), 3.24-3.27(2H,m), 3.57-3.60(2H,m), 3.93-3.97(2H,m), 7.38-7.44(2H,m), 7.46-7.50(1H,m), 7.59(1H,dd,J=8.8 and 2.0Hz), 7.77(1H,dd,J=8.8 and 2.0Hz), 7.91-7.96(3H,m), 8.31(1H,br s), 8.35-8.38(1H,m), 9.26(2H,s).

MS (FAB) m/z: 510 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 512 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-215] 1-[[5-(Pyridin-4-yl)pyrimidin-2-yl]carbonyl]-4-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

15 In a 1N aqueous hydrochloric acid in ethanol was dissolved 1-(tert-butoxycarbonyl)-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine (739 mg), followed by stirring at room temperature for 30 minutes. The solvent was distilled off under reduced pressure. To the residue were added N,N-dimethylformamide (15 ml), triethylamine (2 ml) and 6-trimethylsilylethynylbenzo[b]thiophen-2-sulfonyl chloride (740 mg) and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with methylene chloride, washed with water (thrice), dried over anhydrous sodium sulfate and purified

by chromatography on a silica gel column (hexane : ethyl acetate = 1:0 → 1:1 → ethyl acetate : methylene chloride = 3:1 → 0:1 → methylene chloride : methanol = 100:2 → 100:7), whereby the title compound (167 mg) was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.28 (9H, s), 3.25 (2H, t, J=4.9 Hz), 3.35 (2H, t, J=4.9 Hz), 3.61 (2H, t, J=4.9 Hz), 4.00 (2H, t, J=4.9 Hz), 7.51 (2H, dd, J=4.4, 1.5 Hz), 7.55 (1H, dd, J=8.3, 1.5 Hz), 7.78 (1H, s), 7.83 (1H, d, J=8.3 Hz), 8.00 (1H, s), 8.80 (2H, dd, J=4.4, 1.5 Hz), 9.03 (2H, s).

MS (FAB) m/z: 567 (M+H)<sup>+</sup>.

[Example A-216] 4-[[5-(Pyridin-4-yl)pyrimidin-2-yl]carbonyl]-1-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

In a mixed solvent of tetrahydrofuran (5 ml) and methanol (7 ml) was dissolved 1-[[5-(4-pyridyl)pyrimidin-2-yl]carbonyl]-4-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine (167 mg), followed by the addition of potassium hydroxide (34 mg). The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was made weakly acidic with a saturated aqueous solution of ammonium chloride, and then made weakly alkaline with a saturated aqueous solution of sodium bicarbonate. After concentration under reduced pressure, the concentrate was extracted (4 times) with methylene

chloride. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 1:0 → 24:1). The resulting amorphous was dissolved in methylene chloride, followed by the dropwise addition to hexane to precipitate the resulting mixture as powder. The title compound (112 mg) was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.23(1H,s), 3.25(2H,t,J=5.1Hz), 3.35(2H,t,J=5.1Hz), 3.61(2H,t,J=5.1Hz), 4.00(2H,t,J=5.1Hz), 7.51(2H,dd,J=4.4,1.5Hz), 7.58(1H,dd,J=8.3,0.98Hz), 7.79(1H,s), 7.86(1H,d,J=8.3Hz), 8.02(1H,s), 8.80(2H,dd,J=4.4,1.5Hz), 9.02(2H,s).

MS (FAB) m/z: 490 (M+H)<sup>+</sup>.

[Example A-217] 1-[(5-Chloroisoindolin-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-4, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.22-3.80(8H,m), 4.63-4.65(4H,m), 7.37(1H,d,J=8.3Hz), 7.37(1H,m), 7.43(1H,s), 7.64(2H,d,J=8.3Hz), 8.04(2H,d,J=8.3Hz), 8.20-8.14(2H,br), 8.9(2H,d,J=5.4Hz).

MS (FAB) m/z: 483 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 485 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-218] 4-[4-[4-[(5-Chloroisoindolin-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.25-3.77 (8H,m), 4.62-4.65 (4H,m), 7.33-  
 5 7.39 (2H,m), 7.43 (1H,s), 7.54 (2H,d,J=8.3Hz),  
 7.81 (1H,d,J=6.8Hz), 7.86 (2H,d,J=8.3Hz), 8.28 (2H,d,J=6.8Hz).  
 MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-219] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethyl-  
 1-[[5-pyridin-4-yl]pyrimidin-2-yl]carbonyl]piperazine

10 In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.75 (1.5H,t,J=7.8Hz),  
 0.94 (1.5H,t,J=7.8Hz), 1.60-1.89 (2H,m), 2.23-2.57 (2H,m),  
 3.14 (0.5H,m), 3.25-3.43 (1H,m), 3.45-3.90 (2.5H,m), 4.44-  
 15 4.53 (0.5H,m), 4.65-4.72 (0.5H,m), 7.04 (1H,t,J=2.4Hz),  
 7.34 (1H,dt,J=8.8,2.4Hz), 7.50 (1H,dd,J=8.8,2.4Hz),  
 7.80 (1H,t,J=2.4Hz), 8.18 (2H,br), 8.90 (2H,br),  
 9.39 (2H,t,J=2.4Hz), 12.48 (1H,br).  
 MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example A-220] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethylpiperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

25 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.74 (1.5H,t,J=7.3Hz),

0.93 (1.5H, t, J=7.3Hz), 1.03-1.09 (0.5H, m), 1.58-1.68 (0.5H, m),  
 1.70-1.90 (1.5H, m), 2.13-2.57 (2H, m), 3.13-3.21 (0.5H, m),  
 3.25-3.60 (2H, m), 3.70-3.76 (0.5H, m), 3.78-3.86 (0.5H, m),  
 4.45-4.52 (0.5H, m), 4.67 (0.5H, br), 7.04 (1H, m),  
 5 7.34 (1H, dt, J=8.8, 2.4Hz), 7.50 (1H, dd, J=8.8, 2.4Hz),  
 7.80 (1H, t, J=2.4Hz), 7.90 (2H, dd, J=7.3, 2.4Hz),  
 8.38 (2H, t, J=7.3, 3.4Hz), 9.29 (2H, d, J=4.5Hz), 12.46 (1H, br).  
 MS (FAB) m/z: 517 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 519 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-221] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
 10 2-ethyl-1-[(5-(pyridin-4-yl)pyrimidin-2-  
 yl)carbonyl]piperazine

In the same manner as in Example A-182, the title  
 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.77 (1.5H, t, J=7.8Hz),  
 15 0.95 (1.5H, t, J=7.8Hz), 1.62-1.70 (0.5H, m), 1.73-1.82 (0.5H, m),  
 1.83-1.93 (1H, m), 2.44-2.71 (2H, m), 3.14-3.24 (0.5H, m), 3.35-  
 3.62 (2H, m), 3.67-3.76 (1H, m), 3.79-3.85 (0.5H, m), 4.47-  
 4.53 (0.5H, m), 4.67-4.74 (0.5, m), 7.57-7.62 (1H, m), 8.03-  
 8.14 (4H, m), 8.33-8.37 (1H, m), 8.83 (1H, d, J=4.6Hz),  
 20 9.36 (2H, d, J=3.7Hz).

MS (FAB) m/z: 528 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 530 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-222] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-  
 yl)sulfonyl]-2-ethylpiperazin-1-yl]carbonyl]pyrimidin-5-  
 yl]pyridine N-oxide

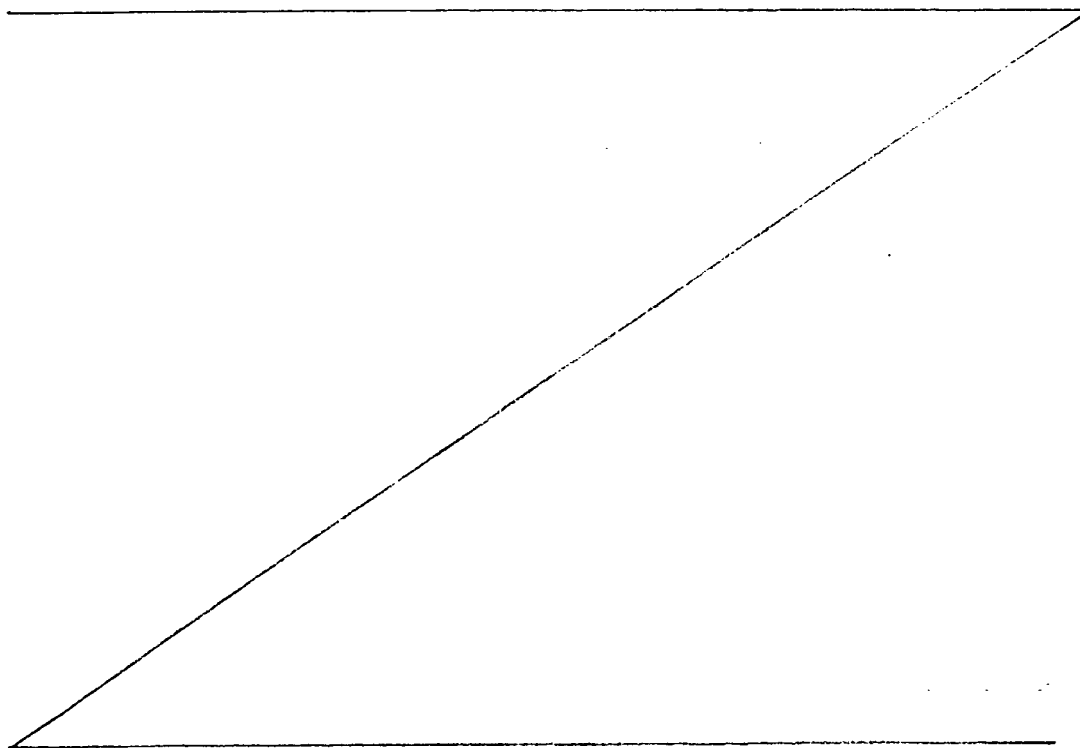
25 In the same manner as in Example A-6, the title  
 compound was obtained.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 0.76 (1.5H, t,  $J=7.3\text{Hz}$ ),  
0.94 (1.5H, t,  $J=7.3\text{Hz}$ ), 1.15-1.28 (0.5H, m), 1.60-1.69 (0.5H, m),  
1.70-1.92 (1.5H, m), 2.50-2.60 (1H, m), 2.62-2.71 (1H, m), 3.12-  
3.24 (0.5H, m), 3.35-3.45 (1H, m), 3.50-3.61 (1H, m), 3.64-  
5 3.87 (1H, m), 4.47-4.54 (0.5H, m), 4.67-4.74 (0.5H, m), 7.58-  
7.63 (1H, m), 7.94-8.00 (2H, m), 8.06-8.13 (2H, m), 8.34-  
8.40 (3H, m), 9.30 (2H, d,  $J=2.0\text{Hz}$ ).

MS (FAB)  $m/z$ : 544  $[(M+H)^+, \text{Cl}^{35}]$ , 546  $[(M+H)^+, \text{Cl}^{37}]$ .

[Example A-223] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethyl-  
10 1-[(5-(pyridin-2-yl)pyrimidin-2-yl)carbonyl]piperazine

In the same manner as in Example A-182, the title  
compound was obtained.



<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.74 (1.5H, t, J=7.3Hz),  
 0.94 (1.5H, t, J=7.3Hz), 1.02-1.13 (0.5H, m), 1.57-1.68 (0.5H, m),  
 1.70-1.89 (2H, m), 2.25-2.49 (1H, m), 3.10-3.23 (0.5H, m), 3.27-  
 3.59 (2.5H, m), 3.68-3.87 (1H, m), 4.45-4.52 (0.5H, m), 4.63-  
 5 4.71 (0.5H, m), 7.03-7.05 (1H, m), 7.32-7.36 (1H, m),  
 7.50 (2H, d, J=8.3, 2.4Hz), 7.79 (1H, br), 7.98-8.02 (1H, m),  
 8.16 (1H, d, J=7.8Hz), 8.75-8.77 (1H, m), 9.48 (2H, br),  
 12.46 (1H, br).

MS (FAB) m/z: 511 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 513 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 [Example A-224] 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-  
 ethylpiperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-  
 oxide

To a methylene chloride solution (50 ml) of 4-[(5-  
 chloroindol-2-yl)sulfonyl]-2-(ethyl)-1-[(5-(pyridin-2-  
 15 yl)pyrimidin-2-yl]carbonyl]piperazine (234 mg) was added  
 metachloroperbenzoic acid (1.58 g) at room temperature.  
 The resulting mixture was stirred for 5 hours. An aqueous  
 solution (20 ml) of sodium sulfite was added, followed by  
 stirring for 1 hour. To the reaction mixture were added a  
 20 saturated aqueous solution of sodium bicarbonate and  
 methylene chloride. The water layer was extracted thrice  
 with methylene chloride. The organic layers were combined,  
 dried over anhydrous sodium sulfate and distilled under  
 reduced pressure to remove the solvent. The residue was  
 25 subjected to chromatography on a silica gel column  
 (methanol : methylene chloride = 1:50). The oil thus

obtained was solidified from ethanol - diethyl ether, whereby the title compound (44.1 mg) was obtained as a pale yellow solid.

MS (FAB) m/z: 527 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 529 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.75 (1.5H, t, J=7.3Hz),  
0.93 (1.5H, t, J=7.3Hz), 1.05-1.13 (0.5H, m), 1.58-1.92 (2.5H, m),  
2.29-2.78 (1H, m), 3.13-3.89 (4H, m), 4.40-4.52 (0.5H, m), 4.62-  
4.71 (0.5H, m), 7.04 (1H, d, J=3.4Hz), 7.32-7.37 (1H, m), 7.47-  
7.55 (3H, m), 7.78-7.82 (1H, m), 7.86-7.90 (1H, m),  
10 8.42 (1H, d, J=5.9Hz), 9.33 (2H, br), 12.44 (1H, br).

[Example A-225] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[5-(pyridin-3-yl)thiazol-2-yl]piperazine

To a solution of 3-(5-thiazolyl)pyridine (400 mg) in diethyl ether (15 mg), n-butyl lithium (a 1.52 N hexane  
15 solution, 1.45 ml) was added dropwise at -78°C. After stirring for 30 minutes, a carbon dioxide gas was blown into the reaction mixture. After 10 minutes, a cooling bath was removed and the temperature of the reaction mixture was allowed to rise back slowly to room  
20 temperature. The reaction mixture was concentrated, whereby the residue of lithium 5-(3-pyridyl)thiazole-2-carboxylate was obtained as a white solid. To a solution of the resulting residue in N,N-dimethylformamide (10 ml) were added 1-[(5-chloroindol-2-yl)sulfonyl]piperazine  
25 hydrochloride (600 mg), 1-hydroxybenzotriazole monohydrate (255 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide



hydrochloride (360 mg) at room temperature. After stirring for 3 days, ethyl acetate (50 ml) and water (100 ml) were added to the reaction mixture. The white precipitate thus obtained was collected by filtration and washed with water and ethyl acetate, whereby the title compound (727 mg) was obtained as a pale brown solid. A portion of the compound was added with an aqueous solution of hydrochloric acid, followed by concentration and drying. The product thus obtained showed the following data.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.32(4H,br s), 3.94(2H,br s), 4.59(2H,br s), 7.20(1H,s), 7.47(1H,d,J=8.8Hz), 7.65(1H,d,J=8.8Hz), 7.66-7.76(1H,m), 7.93(1H,s), 8.36(1H,d,J=8.3Hz), 8.63(1H,br s), 8.78(1H,s), 9.16(1H,s), 12.61(1H,s).

MS (FAB) m/z: 488 (M+H)<sup>+</sup>.

[Example A-226] 3-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.31(4H,br s), 3.93(2H,br s), 4.57(2H,br s), 7.19(1H,s), 7.46(1H,d,J=8.8Hz), 7.50-7.70(2H,m), 7.80(1H,d,J=8.3Hz), 7.92(1H,s), 8.05(1H,s), 8.39(1H,d,J=6.4Hz), 8.67(1H,br s), 8.93(1H,s), 12.61(1H,br s).

MS (FAB)  $m/z$ : 504 (M+H)<sup>+</sup>, 488 (M+H-O)<sup>+</sup>.

[Example A-227] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-4-[5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine

5           A saturated solution of hydrochloride in methanol (12 ml) was added to 1-(t-butoxycarbonyl)-4-[5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine (400 mg) at room temperature. After stirring for 10 minutes, the reaction mixture was concentrated under reduced pressure, whereby 1-

10       [5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine hydrochloride was obtained as a white solid. In a solution of the resulting hydrochloride in methylene chloride (12 ml) was dissolved 5-chloro-1-phenylsulfonylindol-2-sulfonyl chloride (522 mg), followed by the addition of

15       diisopropylethylamine (538  $\mu$ l) at room temperature. After stirring for 3 hours, a saturated aqueous solution (50 ml) of sodium bicarbonate was added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (2 x 15 ml). The organic layers

20       were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 7:1), whereby the title compound (240 mg) was obtained as a foam.

25       <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.63(3H,s), 3.55(2H,s), 3.60(2H,s), 3.92(2H,s), 4.60(2H,s), 7.31(1H,d,J=5.4Hz), 7.35(1H,s),

7.40-7.52 (4H,m), 7.52-7.65 (2H,m), 8.03 (2H,d,J=7.3Hz),  
8.14 (1H,s), 8.23 (1H,d,J=9.3Hz), 8.56 (1H,d,J=5.4Hz).

[Example A-228] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine

5 In the same manner as in Example A-99, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.88 (3H,s), 3.33 (4H,br s), 3.95 (2H,br s), 4.57 (2H,br s), 7.20 (1H,d,J=2.0Hz),  
7.47 (1H,dd,J=8.8,2.0Hz), 7.66 (1H,d,J=8.8Hz),  
10 7.93 (1H,d,J=2.0Hz), 8.32 (1H,d,J=6.4Hz), 8.40 (1H,br s),  
8.94 (1H,d,J=6.4Hz), 9.02 (1H,d,J=2.0Hz), 12.66 (1H,s).  
MS (FAB) m/z: 502 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 504 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-229] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]-2-methylpyridine N-oxide

15

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.28 (4H,br s), 3.47 (3H,s), 3.91 (2H,br),  
4.56 (2H,br s), 7.17 (1H,s), 7.44 (1H,dd,J=8.8,2.0Hz),  
20 7.62 (1H,d,J=8.8Hz), 7.81 (1H,dd,J=6.8,2.7Hz),  
7.90 (1H,d,J=2.0Hz), 8.04 (1H,d,J=2.7Hz), 8.43 (1H,d,J=6.8Hz),  
8.59 (1H,s), 12.57 (1H,br s).  
MS (FAB) m/z: 518 (M+H)<sup>+</sup>, 502 (M+H-O)<sup>+</sup>.

[Example A-230] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[5-(pyridin-4-yl)thiazol-2-yl]piperazine

25

A saturated solution of hydrochloride in methanol (12 ml) was added to 1-(tert-butoxycarbonyl)-4-[5-(pyridin-4-yl)thiazol-2-yl]piperazine (400 mg) at room temperature. After stirring for 1 hour, the reaction mixture was concentrated under reduced pressure, whereby the residue, that is, 1-[5-(pyridin-4-yl)thiazol-2-yl]piperazine hydrochloride was obtained as a white solid. In a solution of the resulting residue in methylene chloride (15 ml) was dissolved [1-phenylsulfonyl-5-(trimethylsilylethynyl)indol-2-yl]sulfonyl chloride (630 mg), followed by the addition of diisopropylethylamine (746  $\mu$ l) at 0 °C. After stirring for 4 hours, methylene chloride (10 ml) and a saturated aqueous solution (30 ml) of sodium bicarbonate were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 6:1), whereby 1-[5-(2-methylpyridin-4-yl)thiazol-2-yl]-4-[[1-phenylsulfonyl-5-(trimethylsilylethynyl)indol-2-yl]sulfonyl]piperazine (214 mg) was obtained as a foam. To a solution of the resulting residue in tetrahydrofuran (10 ml) were added methanol (10 ml), morpholine (54.0  $\mu$ l) and potassium hydroxide (52.0 mg), followed by stirring at room temperature for 3 hours. A saturated aqueous solution

(30 ml) of sodium bicarbonate, methylene chloride (30 ml) and water (10 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (methylene chloride : acetone = 6:1) using silica gel, whereby the title compound (84.8 mg) was obtained as a white solid. The solid was dissolved in tetrahydrofuran, followed by the addition of water. The resulting mixture was concentrated, whereby a white solid was obtained. The solid showed the following data:

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.15(4H,br s), 3.77(2H,br s), 4.01(1H,s), 4.41(2H,br s), 7.05(1H,s), 7.34(1H,d,J=8.5Hz), 7.44(1H,d,J=8.5Hz), 7.72(2H,d,J=4.9Hz), 7.85(1H,s), 8.58(1H,s), 8.63(2H,d,J=4.9Hz), 12.42(1H,br s).

MS (FAB) m/z: 478 (M+H)<sup>+</sup>.

[Example A-231] 4-[2-[[4-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.16(4H,br s), 3.77(2H,br s), 4.02(1H,s), 4.41(2H,br s), 7.06(1H,s), 7.36(1H,d,J=8.5Hz), 7.46(1H,d,J=8.5Hz), 7.78(2H,d,J=6.9Hz), 7.86(1H,s),

8.26(2H,d,J=6.9Hz), 8.48(1H,s), 12.43(1H,br s).

MS (FAB) m/z: 494 (M+H)<sup>+</sup>, 478 (M+H-O)<sup>+</sup>.

[Example A-232] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine  
5 hydrochloride

In the same manner as in Example A-7, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.14(4H,br s), 3.79(2H,br s),

4.41(2H,br s), 7.71(1H,dd,J=8.8,2.0Hz),

10 7.83(1H,dd,J=8.8,2.0Hz), 8.11(2H,d,J=5.9Hz),

8.15(1H,d,J=8.8Hz), 8.22(1H,d,J=2.0Hz), 8.25(1H,d,J=8.8Hz),

8.51(1H,s), 8.77(1H,s), 8.79-8.85(2H,m).

MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-233] 4-[2-[[4-[(6-Chloronaphthalen-2-  
15 yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine  
N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.13(4H,br s), 3.77(2H,br s),

20 4.43(2H,br s), 7.69(1H,d,J=8.8Hz), 7.76(2H,d,J=6.4Hz),

7.82(1H,d,J=8.8Hz), 8.15(1H,d,J=8.8Hz), 8.20-8.28(5H,m),

8.46(1H,s), 8.50(1H,s).

MS (FAB) m/z: 515 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 517 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-234] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
25 [[5-(pyridin-2-yl)thiazol-2-yl]carbonyl]piperazine

hydrochloride

In the same manner as in Example A-4, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.13(4H, br s), 3.77(2H, br s),  
 5 4.42(2H, br s), 7.37(1H, m), 7.69(1H, dd, J=8.8, 2.0Hz),  
 7.81(1H, d, J=8.8Hz), 7.89(1H, m), 8.03(1H, d, J=7.8Hz),  
 8.15(1H, d, J=8.8Hz), 8.21(1H, d, J=2.0Hz), 8.25(1H, d, J=8.8Hz),  
 8.50(1H, s), 8.56(1H, s), 8.57(1H, d, J=4.4Hz).

MS (FAB) m/z: 499 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 501 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 [Example A-235] 2-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine  
 N-oxide

In the same manner as in Example A-6, the title compound was obtained.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.14(4H, br s), 3.78(2H, br s),  
 4.41(2H, br s), 7.47(1H, t, J=7.8Hz), 7.54(1H, t, J=7.8Hz),  
 7.68(1H, dd, J=8.8, 2.0Hz), 7.84(1H, d, J=8.8Hz),  
 8.15(1H, d, J=8.8Hz), 8.20(1H, s), 8.25(1H, d, J=8.8Hz), 8.42-  
 8.51(3H, m), 8.95(1H, s).

20 MS (FAB) m/z: 515 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 517 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-236] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine  
 hydrochloride

In the same manner as in Example A-4, the title  
 25 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.18(4H, br s), 3.80(2H, br s),  
4.41(2H, br s), 7.04(1H, s), 7.30(1H, dd, J=8.8, 1.5Hz),  
7.49(1H, d, J=8.8Hz), 7.76(1H, s), 8.15(2H, d, J=5.9Hz),  
8.79(1H, s), 8.84(2H, d, J=5.9Hz), 12.44(1H, s).

5 MS (FAB) m/z: 488 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 490 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-237] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine  
N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.16(4H, br s), 3.78(2H, br s),  
4.43(2H, br s), 7.03(1H, s), 7.30(1H, dd, J=8.8, 2.0Hz),  
7.47(1H, d, J=8.8Hz), 7.75(1H, d, J=2.0Hz), 7.77(2H, d, J=7.3Hz),  
8.25(2H, d, J=7.3Hz), 8.30(1H, s), 8.47(1H, s), 12.41(1H, s).

15 MS (FAB) m/z: 504 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 506 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-238] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
4-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine  
hydrochloride

20 In the same manner as in Example A-4, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.24(4H, br s), 3.84(2H, br s),  
4.46(2H, br s), 7.50-7.65(3H, m), 8.03-8.10(2H, m),  
8.30(1H, s), 8.76(1H, s), 8.80(2H, m).

MS (FAB) m/z: 505 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 507 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

25 [Example A-239] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-



yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine  
N-oxide

In the same manner as in Example A-6, the title  
compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.22 (4H, br s), 3.82 (2H, br s),  
4.47 (2H, br s), 7.54 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.78 (2H, d,  $J=7.3\text{Hz}$ ),  
8.05 (1H, d,  $J=8.8\text{Hz}$ ), 8.09 (1H, s), 8.25 (2H, d,  $J=7.3\text{Hz}$ ),  
8.29 (1H, s), 8.48 (1H, s).

MS (FAB)  $m/z$ : 521  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 523  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 [Example A-240] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[3-  
(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine  
hydrochloride

Ethyl 3-(pyridin-4-yl)-1,2,4-triazin-6-carboxylate  
(200 mg) was dissolved in a mixed solvent of  
15 tetrahydrofuran (5 ml) and methanol (5 ml) at room  
temperature. A 1N aqueous solution (1.00 ml) of sodium  
hydroxide was added to the reaction mixture in one portion.  
After stirring for 5 minutes, the reaction mixture was  
distilled under reduced pressure to remove tetrahydrofuran  
and methanol, followed by neutralization with 1N  
20 hydrochloric acid. The reaction mixture was concentrated  
to dryness, whereby 3-(pyridin-4-yl)-1,2,4-triazine-6-  
carboxylic acid was obtained as a crudely purified product.

In N,N-dimethylformamide (10 ml) were suspended 3-  
25 (pyridin-4-yl)-1,2,4-triazine-6-carboxylic acid and 1-[(5-  
chloroindol-2-yl)sulfonyl]piperazine hydrochloride (292 mg)

at room temperature. To the reaction mixture were successively added 1-hydroxybenzotriazole (117 mg), N-methylmorpholine (191  $\mu$ l) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250 mg), followed by stirring overnight. After completion of the reaction, the solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the residue to separate into layers. The organic layer was dried over magnesium sulfate and the filtrate was concentrated. Ethanol was added to the residue. Yellow crystals thus precipitated were collected by filtration and dried, whereby the free form (282 mg) of the title compound was obtained. The free form was suspended in ethanol and the resulting suspension was made acidic by the addition of 1N hydrochloric acid (in ethanol) and a small amount of water. After concentration of the resulting solution, ethanol and ethyl acetate were added and the resulting mixture was concentrated again. Crystals thus precipitated were collected by filtration and dried, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.05-3.09(2H,m), 3.18-3.21(2H,m), 3.69-3.72(2H,m), 3.84-3.88(2H,m), 7.05(1H,d,J=1.5Hz), 7.33(1H,dd,J=8.8,2.0Hz), 7.50(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz), 8.45-8.52(2H,m), 8.92-8.98(2H,m), 9.17(1H,d,J=1.0Hz), 12.47(1H,s).

MS (FAB)  $m/z$ : 484  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 486  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-241] 4-[6-[[4-[(5-Chloroindol-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2,4-triazin-3-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

5  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.06(2H,br), 3.18(2H,br), 3.70(2H,br), 3.85(2H,br), 7.05(1H,s), 7.32(1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.49(1H,d,  $J=8.8\text{Hz}$ ), 7.79(1H,d,  $J=2.0\text{Hz}$ ), 8.34(2H,d,  $J=7.3\text{Hz}$ ), 8.40(2H,d,  $J=7.3\text{Hz}$ ), 9.06(1H,s), 12.45(1H,s).  
MS (FAB)  $m/z$ : 500  $[(M+H)^+, \text{Cl}^{35}]$ , 502  $[(M+H)^+, \text{Cl}^{37}]$ .

10 [Example A-242] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2,5-dihydro-5-oxo-6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example A-4, the title compound was obtained.

15  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.00-3.09(2H,m), 3.10-3.17(2H,m), 3.75-3.81(4H,m), 7.74(1H,dd,  $J=8.8$  and  $2.0\text{Hz}$ ), 7.86(1H,d,  $J=8.8\text{Hz}$ ), 8.20(1H,d,  $J=8.8\text{Hz}$ ), 8.25-8.35(4H,m), 8.55(1H,br s), 8.86(2H,d,  $J=5.4\text{Hz}$ ).  
MS (FAB)  $m/z$ : 511  $[(M+H)^+, \text{Cl}^{35}]$ , 513  $[(M+H)^+, \text{Cl}^{37}]$ .

20 [Example A-243] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(2,6-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example A-182, the title compound was obtained.

25  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.71(6H,s), 2.94(2H,br s), 3.13(2H,br

s), 3.37(2H,br s), 3.80(2H,br s), 7.74(1H,dd,J=8.8,2.0Hz), 7.83(1H,d,J=8.8Hz), 8.13(2H,br s), 8.13(1H,d,J=8.8Hz), 8.27-8.30(2H,m), 8.52(1H,s), 9.38(2H,s).

MS (FAB) m/z: 522 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 524 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example A-244] 4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,6-dimethylpyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.61(6H,s), 3.15(2H,d,J=4.8Hz), 3.26(2H,d,J=4.8Hz), 3.57(2H,d,J=4.8Hz), 3.96(2H,d,J=4.9Hz), 7.37(2H,s), 7.60(1H,dd,J=8.8,2.0Hz), 7.76(1H,dd,J=8.8,1.5Hz), 7.91-7.97(3H,m), 8.31(1H,s), 8.96(2H,s).

15 MS (FAB) m/z: 538 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 540 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-245] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine

A saturated solution of hydrochloride in methanol (10 ml) was added to 1-(tert-butoxycarbonyl)-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine (180 mg). After stirring for 30 minutes, the solvent was distilled off under reduced pressure. To the residue were added methylene chloride (10 ml), 5-chloro-1-phenylsulfonylindol-2-sulfonyl chloride (260 mg) and diisopropylethylamine (235 µg) at room temperature. After stirring for 4 hours, methylene chloride (10 ml) and a saturated aqueous solution (30 ml)

of sodium bicarbonate were added the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 5:1 → 3:1), whereby the title compound (131 mg) was obtained as a pale yellow foam.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.18(4H,s), 3.57(4H,s), 7.37-7.46(4H,m), 7.50-7.59(4H,m), 7.80(2H,d,J=8.3Hz), 7.85(2H,d,J=8.3Hz), 7.86(2H,d,J=8.3Hz), 8.12(1H,d,J=8.8Hz), 8.76(2H,br d,J=4.4Hz).

[Example A-246] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine hydrochloride

In the same manner as in Example A-103, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.05(4H,br t,J=4.0Hz), 3.18(4H,br t,J=4.0Hz), 6.97(1H,d,J=1.5Hz), 7.16(1H,dd,J=8.8,1.9Hz), 7.40(1H,d,J=8.8Hz), 7.68(1H,d,J=1.9Hz), 7.83(2H,d,J=8.5Hz), 8.09(2H,d,J=8.5Hz), 8.19(2H,d,J=6.6Hz), 8.97(2H,d,J=6.6Hz), 12.40(1H,br s).

MS (FAB) m/z: 517 (M+H)<sup>+</sup>.

[Example A-247] 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]sulfonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title

compound was obtained.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.00 (4H, br t,  $J=4.6\text{Hz}$ ), 3.17 (4H, br t,  $J=4.0\text{Hz}$ ), 6.96 (1H, s), 7.18 (1H, dd,  $J=9.1, 1.7\text{Hz}$ ), 7.39 (1H, d,  $J=9.1\text{Hz}$ ), 7.69 (1H, d,  $J=1.7\text{Hz}$ ), 7.73 (2H, d,  $J=8.3\text{Hz}$ ), 7.82 (2H, d,  $J=6.8\text{Hz}$ ), 7.93 (2H, d,  $J=8.3\text{Hz}$ ), 8.34 (2H, d,  $J=6.8\text{Hz}$ ), 12.35 (1H, br s).

MS (FAB)  $m/z$ : 533 ( $M+H$ ) $^+$ .

[Example A-248] 1-[(5-Chloroindol-2-yl)carbonyl]-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine hydrochloride

A saturated solution of hydrochloride in methanol (10 ml) was added to 1-(tert-butoxycarbonyl)-4-[4-(pyridin-4-yl)phenylsulfonyl]piperazine (180 mg). After stirring for 30 minutes, the solvent was distilled off under reduced pressure. To a solution of the residue in  $N,N$ -dimethylformamide (10 ml) were added (5-chloroindol-2-yl)carboxylic acid (90.0 mg), 1-hydroxybenzotriazole (75.5 mg) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (107 mg) and diisopropylethylamine (233  $\mu\text{g}$ ) at room temperature. After stirring for 3 days, methylene chloride (100 ml) and water (500 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (50 ml). The organic layers were combined, washed with water (500 ml) and a saturated aqueous solution (100 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The

residue was purified by chromatography on a silica gel column (silica gel: 20 g, methylene chloride : acetone = 3:1 → 1:1), whereby the title compound (97.5 mg) was obtained as a white solid. The resulting compound was dissolved in hydrochloric acid - methanol - methylene chloride - tetrahydrofuran, followed by concentration, whereby the title compound was obtained.

Hydrochloride:

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.10(4H, br s), 3.84(4H, br s), 6.76(1H, d, J=1.5Hz), 7.17(1H, dd, J=8.8, 2.0Hz), 7.39(1H, d, J=8.8Hz), 7.62(1H, d, J=2.0Hz), 7.96(2H, d, J=8.3Hz), 8.22(2H, d, J=8.3Hz), 8.30(2H, d, J=6.4Hz), 8.97(2H, d, J=6.4Hz), 11.76(1H, br s).

MS (FAB) m/z: 481 (M+H)<sup>+</sup>.

[Example A-249] 4-[4-[[4-[(5-Chloroindol-2-yl)carbonyl]piperazin-1-yl]sulfonyl]phenyl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.07(4H, br s), 3.83(4H, br s), 6.75(1H, s), 7.18(1H, br d, J=8.8Hz), 7.39(1H, d, J=8.8Hz), 7.62(1H, br s), 7.85(2H, d, J=8.3Hz), 7.88(2H, d, J=6.6Hz), 8.07(2H, d, J=8.3Hz), 8.33(2H, d, J=6.6Hz), 11.74(1H, br s).

MS (FAB) m/z: 497 (M+H)<sup>+</sup>.

[Example A-250] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(5-(pyridin-4-yl)pyrimidin-2-yl)carbonyl]-2-(2-

methlpropyl)piperazine

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.84-1.62 (2H,m), 1.75 (3H,s),  
 1.77 (3H,s), 2.26-2.41 (1H,m), 2.55-2.70 (1H,m), 3.18-  
 3.50 (2H,m), 3.55-3.68 (1H,m), 3.70-4.45 (2H,m), 5.36-  
 5.58 (1H,m), 7.04 (1H,s), 7.34 (1H,d,J=8.8Hz),  
 7.51 (1H,d,J=8.8Hz), 7.80 (1H,s), 8.16 (2H,br), 8.90 (2H,br),  
 9.37 (2H,s), 12.48 (1H,br).

MS (FAB) m/z: 539 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 541 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-251] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
 1-[(5-(pyridin-4-yl)pyrimidin-2-yl)carbonyl]-2-(2-  
 methylpropyl)piperazine

In the same manner as in Example A-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.64-1.68 (3H,m), 1.75 (3H,s),  
 1.77 (3H,s), 2.25-2.58 (1H,m), 2.60-2.83 (1H,m), 2.87-  
 4.23 (4H,m), 4.40-4.53 (1H,m), 7.06 (1H,s),  
 7.34 (1H,d,J=8.8Hz), 7.49 (1H,d,J=8.8Hz), 7.81 (1H,s),  
 8.15 (2H,br), 8.88 (2H,br), 9.37 (2H,br), 12.48 (1H,s).

MS (FAB) m/z: 556 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 558 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-252] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,2-  
 dimethyl-4-[4-(pyridin-4-yl)benzoyl]piperazine

In the same manner as in Example A-4, the title compound was obtained.



<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.14 (3H, br s), 1.28 (3H, br s), 3.20-3.90 (6H, br), 7.53-7.70 (2H, br), 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.90 (1H, br), 7.96-8.08 (2H, m), 8.14 (1H, d, J=8.8 Hz), 8.20-8.33 (4H, m), 8.57 (1H, s), 8.92 (2H, br).

5 MS (FAB) m/z: 520 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 522 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-253] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-3,3-dimethylpiperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.26 (3H, br), 1.39 (3H, br), 3.26 (1H, br), 3.50-3.95 (5H, br), 7.45-7.55 (4H, br), 7.58 (1H, dd, J=8.8, 2.0 Hz), 7.62 (2H, d, J=7.8 Hz), 7.79 (1H, d, J=7.8 Hz), 7.89 (2H, d, J=7.8 Hz), 7.92 (1H, s), 8.27 (2H, br), 8.37 (1H, s).

15 MS (FAB) m/z: 536 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 538 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-254] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,2-dimethyl-1-[4-(pyridin-4-yl)benzoyl]piperazine

20 In the same manner as in Example A-26, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.50 (6H, s), 3.10 (2H, s), 3.20-3.30 (2H, br t), 3.50 (2H, br), 7.58 (2H, d, J=7.8 Hz), 7.73 (1H, dd, J=8.8, 2.0 Hz), 7.87 (1H, dd, J=8.8, 2.0 Hz), 7.98 (2H, d, J=7.8 Hz), 8.19 (1H, d, J=8.8 Hz), 8.20-8.30 (3H, m), 8.30 (1H, d, J=7.8 Hz), 8.53 (1H, s), 8.90 (2H, d, J=5.9 Hz).

25

MS (FAB)  $m/z$ : 520  $[(M+H)^+, Cl^{35}]$ , 522  $[(M+H)^+, Cl^{37}]$ .

[Example A-255] 4-[4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2,2-dimethylpiperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

5 In the same manner as in Example A-6, the title compound was obtained.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.60 (5H, br), 3.04 (2H, s),  
3.20 (2H, t,  $J=4.9$ Hz), 3.48 (2H, t,  $J=4.9$ Hz), 7.40-7.50 (4H, m),  
7.56 (2H, d,  $J=8.8$ Hz), 7.61 (1H, dd,  $J=8.8, 2.0$ Hz),  
10 7.79 (1H, dd,  $J=8.8, 2.0$ Hz), 7.88-7.96 (1H, m),  
7.95 (2H, d,  $J=7.8$ Hz), 8.25 (2H, d,  $J=7.8$ Hz), 8.34 (1H, s).

MS (FAB)  $m/z$ : 536  $[(M+H)^+, Cl^{35}]$ , 538  $[(M+H)^+, Cl^{37}]$ .

[Example A-256] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)-1-[[4-(pyridin-4-yl)-3-cyclohexen-  
15 1-yl]carbonyl]piperazine

In a mixture of methylene chloride (30 mL) and N,N-dimethylformamide (30 mL) was dissolved 4-(pyridin-4-yl)-3-hexenic acid hydrochloride (480 mg). Under ice cooling, 1-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)piperazine (1.024 g), 1-hydroxybenzotriazole (405 mg), N-methylmorpholine (607 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (575 mg) were added to the resulting  
20 solution. After 10 minutes, the mixture was allowed to  
25 rise back to room temperature, followed by stirring. After 48 hours, the reaction was terminated and the solvent was

distilled off under reduced pressure. Ethyl acetate was added to the residue. The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate and saturated saline, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methylene chloride : methanol = 20:1), whereby the title compound (680 mg, colorless oil) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.14 (1H, t,  $J=7.1\text{Hz}$ ), 1.22 (1H, t,  $J=7.1\text{Hz}$ ), 1.64-3.87 (14H, m), 3.69 (3H, s), 6.33-6.42 (1H, m), 6.97 (1H, m), 7.21-7.40 (4H, m), 7.67 (1H, d,  $J=2\text{Hz}$ ), 8.54 (2H, m).

MS (FAB)  $m/z$ : 557 ( $\text{M}+\text{H}$ ) $^+$ .

[Example A-257] Sodium [4-[(5-chloroindol-2-yl)sulfonyl]-1-[[4-(pyridin-4-yl)-3-cyclohexen-1-yl]carbonyl]piperazin-2-yl]acetate

In a 100-mL egg-plant type flask was charged 4-[(5-chloroindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)-1-[[4-(pyridin-4-yl)-3-hexen-1-yl]carbonyl]piperazine (680 mg), followed by dissolution in methanol (20 mL). A 1N sodium hydroxide solution (5 mL) was added to the resulting solution and the resulting mixture was stirred at 70°C. After 23 hours, the reaction was terminated. After concentration, the crystals were collected by filtration, whereby the title compound (320 mg, colorless solid) was obtained as a sodium salt.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.10-3.90 (16H, m), 6.40-6.48 (1H, m),

6.95 (1H, d, J=2.9Hz), 7.19 (1H, dd, J=8.8, 2.0Hz), 7.41 (3H, m),  
7.64 (1H, d, J=2.5Hz), 8.40 (2H, m).

[Example A-258] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-  
[(piperidin-1-yl)carbonylmethyl]-1-[[4-(pyridin-4-yl)-3-  
5 cyclohexen-1-yl]carbonyl]piperazine

In the same manner as in Example A-4, the title  
compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.61-3.82 (24H, m), 4.65-4.93 (2H, m), 6.96-  
7.68 (5H, m), 8.02 (1H, s), 8.51 (2H, m).

10 [Example A-259] 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-  
[(piperidin-1-yl)carbonylmethyl]piperazin-1-yl]carbonyl]-1-  
cyclohexen-1-yl]pyridine N-oxide

In the same manner as in Example A-6, the title  
compound was obtained.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.63-4.94 (26H, m), 6.28 (1H, m),  
6.99 (1H, m), 7.18-7.40 (4H, m), 7.65 (1H, d, J=15.4Hz),  
8.13 (1H, d, J=4.9Hz).

MS (FAB) m/z: 626 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

[Example A-260] 1-[(E)-4-Chloro-2-  
20 methoxystyryl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-  
yl]carbonyl]piperazine hydrochloride

In the same manner as in Example A-105, the title  
compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.07 (2H, br), 3.24 (2H, br), 3.39 (2H, br),  
25 3.82 (2H, br), 3.92 (2H, s), 7.10 (1H, dd, J=8.3, 1.5Hz),

7.23 (1H, d, J=1.5 Hz), 7.29 (1H, d, J=15.6 Hz),  
7.56 (1H, d, J=15.6 Hz), 7.84 (1H, d, J=8.3 Hz),  
8.34 (2H, d, J=6.1 Hz), 8.98 (2H, d, J=6.1 Hz), 9.46 (2H, s).  
MS (FAB) m/z: 500 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 502 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example A-261] 1-[((E)-4-Chloro-2-hydroxystyryl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride

In methylene chloride (18 ml) was dissolved 1-[((E)-4-chloro-2-methoxystyryl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine (366 mg), followed by  
10 the addition of boron tribromide (a 1.0 mole solution, methylene chloride) at -78°C in an argon atmosphere. The resulting mixture was stirred at -78°C for 0.5 hour and 0°C for 2 hours. The reaction mixture was distilled under  
15 reduced pressure. After a saturated aqueous solution of sodium bicarbonate and water were added to the residue and the insoluble matter was filtered off, methylene chloride was added for extraction. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate  
20 and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (10% methanol - methylene chloride) using as a carrier silica gel and then chromatography on a silica gel column (methylene chloride ~ 5% methanol - methylene chloride),  
25 whereby a crudely purified product (146 mg) was obtained. A portion (81.0 mg) of the product was dissolved in

tetrahydrofuran. To the resulting solution was added 1N aqueous hydrochloric acid in ethanol. The resulting mixture was solidified, followed by collection by filtration. The resulting solid was then dissolved in methanol. After filtration of the resulting solution, water was added. The solvent was distilled off under reduced pressure, whereby the title compound (68.5 g) was obtained as colorless powder.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.00-3.10 (2H,m), 3.20-3.25 (2H,m), 3.35-3.45 (2H,m), 3.80-3.85 (2H,m), 6.94 (1H,d,J=8.3Hz), 7.05 (1H,s), 7.24 (1H,d,J=15.6Hz), 7.55 (1H,d,J=15.6Hz), 7.74 (1H,d,J=8.3Hz), 8.36 (2H,br s), 8.95-9.05 (2H,m), 9.47 (2H,s), 11.10 (1H,br s).

MS (FAB) m/z: 486 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 488 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-262] 4-[2-[[4-[(E)-4-Chloro-2-hydroxystyryl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-105, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.00-3.10 (2H,m), 3.15-3.25 (2H,m), 3.35-3.40 (2H,m), 3.75-3.85 (2H,m), 6.90-7.00 (2H,m), 7.23 (1H,d,J=15.6Hz), 7.54 (1H,d,J=15.6Hz), 7.74 (1H,d,J=8.3Hz), 7.97 (2H,d,J=7.8Hz), 8.45-50 (2H,m), 9.32 (2H,s), 10.95 (1H,br s).

MS (FAB) m/z: 502 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 504 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-263] 2,cis-6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

In the same manner as in Example A-105, the title  
5 compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.50-2.80 (3H,m), 2.95-3.05 (2H,m), 3.10-  
3.20 (1H,m), 3.65-3.75 (1H,m), 3.68 (3H,s), 3.75 (3H,s), 4.00-  
4.10 (1H,m), 4.15-4.25 (1H,m), 5.15-5.25 (1H,m), 7.40-  
7.50 (2H,m), 7.55-7.60 (1H,m), 7.70-7.75 (1H,m), 7.90-  
10 7.95 (3H,m), 8.30 (1H,s), 8.75-8.85 (2H,m), 8.96 (2H,s).

[Example A-264] 2,cis-6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

In tetrahydrofuran (10 ml) and methanol (5 ml) were  
15 dissolved 2,cis-6-bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine (372 mg), followed by the  
dropwise addition of a mixture of sodium hydroxide (310 ml)  
and water (1.6 ml) under ice cooling. The resulting  
20 mixture was stirred at room temperature for 23.5 hours.  
After concentrated hydrochloric acid was added to the  
reaction mixture to make it acidic, the solvent was  
distilled off under reduced pressure. The residue was  
suspended in N,N-dimethylformamide (15 ml), followed by the  
25 addition of di-tert-butyl dicarbonate (665 mg), pyridine  
(290 µl) and ammonium bicarbonate (304 mg) under ice

cooling. The resulting mixture was stirred at room temperature for 19 hours. After completion of the the stirring, the solvent was distilled off under reduced pressure. The residue was subjected to chromatography on a silica gel column (methylene chloride ~ 20% methanol - methylene chloride), whereby a crudely purified product (182 mg) was obtained. A 62.3 mg portion of the resulting product was subjected to chromatography on a silica gel column (methylene chloride ~ 15% methanol - methylene chloride). The solvent was then distilled off under reduced pressure. Ethyl acetate was added to the residue to solidify the same, whereby the title compound (23 mg) was obtained as pale yellow powder.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.25-2.35 (1H,m), 2.40-2.60 (3H,m), 2.80-3.00 (2H,m), 3.50-3.60 (1H,m), 3.8-3.95 (2H,m), 4.90-5.00 (1H,m), 6.90 (1H,br s), 7.06 (1H,br s), 7.45 (1H,br s), 7.53 (1H,br s), 7.70-7.75 (1H,m), 7.75-7.85 (1H,m), 7.85-7.95 (2H,m), 8.17 (1H,d,J=8.8Hz), 8.25-8.35 (2H,m), 8.51 (1H,s), 8.70-8.75 (1H,m), 9.31 (2H,s).

MS (FAB)  $m/z$ : 608  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 610  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-265] 4-[2-[[2,cis-6-Bis(carbamoylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.



<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.25-2.35 (1H,m), 2.40-2.60 (3H,m), 2.80-3.00 (2H,m), 3.55-3.60 (1H,m), 3.85-3.95 (2H,m), 4.90-5.00 (1H,m), 6.89 (1H,br s), 7.06 (1H,br s), 7.43 (1H,br s), 7.51 (1H,br s), 7.70-7.75 (1H,m), 7.75-7.85 (1H,m),  
 5 7.97 (2H,d,J=7.3Hz), 8.16 (1H,d,J=8.8Hz), 8.20-8.40 (4H,m), 8.51 (1H,s), 9.29 (2H,s).

MS (FAB) m/z: 624 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 626 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-266] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine  
 10

In the same manner as in Example A-105, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.45-3.30 (6H,m), 3.50-5.40 (6H,m), 3.67, 3.74 (3H,each s), 7.45-7.50 (2H,m), 7.55-7.65 (1H,m), 7.70-7.80 (1H,m), 7.90-7.95 (3H,m), 8.29 (1H,br s),  
 15 8.78 (2H,d,J=5.4Hz), 8.99, 9.00 (2H,each s).

[Example A-267] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

20 In tetrahydrofuran (10 ml) and methanol (5.0 ml) was dissolved 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine (583 mg). Under ice cooling, a mixture of sodium hydroxide (200 mg) and water (1.0 ml) was added.  
 25 dropwise to the resulting solution under ice cooling, followed by stirring at room temperature for 5 hours.

Under ice cooling, concentrated hydrochloric acid (420  $\mu$ l) was added to the reaction mixture to make it weakly acidic. The reaction mixture was then distilled under reduced pressure. To the residue were added morpholine (102  $\mu$ l),  
5 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (239 mg) and 1-hydroxybenzotriazole hydrate (159 mg). The resulting mixture was dissolved in N,N-dimethylformamide (60 ml) and methylene chloride (30 ml). Diisopropylethylamine (760  $\mu$ l) was added dropwise to the  
10 resulting solution under ice cooling, followed by stirring at room temperature for 12.5 hours. The reaction mixture was distilled under reduced pressure. A 100% aqueous solution of citric acid was added to the residue and it was extracted with methylene chloride. The organic layer was  
15 washed with a saturated aqueous solution of sodium bicarbonate and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (10% methanol - methylene  
20 chloride) using as a carrier silica gel, followed by crystallization from methylene chloride - tetrahydrofuran, whereby a crudely purified product (349 mg) was obtained. A portion (161 mg) of the product was dissolved in methylene chloride - methanol. To the resulting solution  
25 was added 1N aqueous hydrochloride in ethanol (260  $\mu$ l) and the mixture was concentrated to dryness. Ethyl acetate was

added to the concentrate and the solid thus obtained was collected by filtration, washed with ethyl acetate and dried, whereby the title compound (117 mg) was obtained as colorless powder.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.25-5.15 (17H,m), 7.70-7.75 (1H,m), 7.82 (1H,d,J=8.8Hz), 8.15-8.30 (5H,m), 8.51 (1H,br s), 8.90-9.00 (2H,m), 9.35-9.45 (2H,m).

MS (FAB)  $m/z$ : 621  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 623  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-268] 2,cis-6-Bis[(N-methylcarbamoyl)methyl]-4-  
10 [(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

In the same manner as in Example A-264, the title compound was obtained.

15  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.20-2.70 (10H,m), 2.70-2.90 (2H,m), 3.40-4.10 (3H,m), 4.90-5.00 (1H,m), 7.73 (1H,d,J=7.8Hz), 7.81 (1H,d,J=7.8Hz), 7.94 (1H,d,J=4.4Hz), 8.01 (1H,d,J=4.4Hz), 8.17 (1H,d,J=8.3Hz), 8.20-8.40 (4H,m), 8.52 (1H,s), 8.98 (2H,d,J=5.9Hz), 9.43 (2H,s).

MS (FAB)  $m/z$ : 636  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 638  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

20 [Example A-269] 2,cis-6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

25 In the same manner as in Example A-264, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.50-3.10 (6H,m), 2.73 (3H,s),  
 2.86 (3H,s), 2.97 (3H,s), 3.04 (3H,s), 3.53 (1H,d,J=11.7Hz),  
 3.84 (1H,d,J=12.2Hz), 3.99 (1H,d,J=9.8Hz),  
 5.02 (1H,d,J=10.8Hz), 7.71 (1H,dd,J=9.0,2.2Hz),  
 5 7.79 (1H,dd,J=8.5,1.7Hz), 8.17 (1H,d,J=8.8Hz), 8.20-  
 8.35 (4H,m), 8.51 (1H,s), 8.90-8.95 (2H,m), 9.35-9.45 (2H,m).  
 MS (FAB) m/z: 664 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 666 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-270] 4-[2-[[4-[(6-Chloronaphthalen-2-  
 yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazin-  
 10 1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title  
 compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.25-5.15 (17H,m), 7.70-7.75 (1H,m), 7.80-  
 7.85 (1H,m), 7.90-8.00 (2H,m), 8.18 (1H,d,J=8.8Hz), 8.20-  
 15 8.30 (2H,m), 8.30-8.40 (2H,m), 8.49 (1H,br s),  
 9.26 (2H,d,J=7.8Hz).

MS (FAB) m/z: 637 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 639 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-271] 4-[2-[[2,cis-6-Bis(N,N-  
 dimethylcarbamoylmethyl)-4-(6-chloronaphthalen-2-  
 20 ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine  
 N-oxide

In the same manner as in Example A-6, the title  
 compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.50-3.30 (6H,m), 2.91 (3H,m), 3.00 (3H,m),  
 25 3.08 (3H,m), 3.12 (3H,m), 3.70 (1H,d,J=12.2Hz),

4.16 (1H, d, J=12.7Hz), 4.37 (1H, d, J=10.7Hz), 5.20-5.30 (1H, m),  
 7.50 (2H, d, J=7.3Hz), 7.57 (1H, dd, J=8.8, 2.0Hz),  
 7.72 (1H, dd, J=8.6, 1.7Hz), 7.85-7.95 (3H, m), 8.25-8.35 (3H, m),  
 8.91 (2H, s).

5 MS (FAB) m/z: 680 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 682 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-272] 4-[2-[[2, cis-6-Bis(N-methylcarbamoylmethyl)-4-(6-chloronaphthalen-2-ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

10 In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 2.50-2.80 (4H, m), 2.66 (3H, s), 2.78 (3H, s),  
 2.90-3.00 (2H, m), 3.64 (1H, d, J=12.7Hz), 4.01 (1H, d, J=12.2Hz),  
 4.20 (1H, d, J=9.8Hz), 5.10-5.15 (1H, m),  
 15 7.62 (1H, dd, J=8.8, 2.0Hz), 7.78 (1H, dd, J=8.8, 1.5Hz),  
 7.97 (2H, d, J=7.3Hz), 8.00-8.10 (3H, m), 8.35-8.45 (3H, m),  
 9.20 (2H, s).

MS (FAB) m/z: 652 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 654 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example A-273] 2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

In the same manner as in Example A-105, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.84, 1.09 (9H, each s), 2.10-2.20 (2H, m),  
 25 2.35-2.65 (2H, m), 3.15-5.25 (7H, m), 7.10-7.80 (14H, m), 7.85-

8.00 (3H,m), 8.20-8.30 (1H,m), 8.65-9.00 (4H,m).

MS (FAB) m/z: 776 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 778 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-274] 4-(6-Chloronaphthalen-2-ylsulfonyl)-2-(2-hydroxyethyl)-1-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride

In pyridine (6.0 ml) was dissolved 2-[(tert-butyl diphenylsilyloxy)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine (150 mg). A hydrogen fluoride - pyridine complex (2.0 ml) was added dropwise to the resulting solution under ice cooling, followed by stirring at 0°C for 1.5 hours. Ethyl acetate (40 ml) was added to the reaction mixture to dilute it. Then, the diluted mixture was poured into ice. The resulting mixture was extracted. The organic layer was washed with saturated saline, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (5% methanol - methylene chloride ~ 10% methanol - methylene chloride) using as a carrier silica gel, whereby a crudely purified product (97.9 mg) was obtained. The resulting product was dissolved in methylene chloride, followed by the addition of 1N hydrochloric acid in ethanol (182 µl) for solidification. Tetrahydrofuran was added to the residue to solidify the same, whereby the title compound (62.7 mg) was obtained as colorless crystalline powder.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.20-5.20 (9H,m), 6.90-7.05 (1H,m), 7.50-7.60 (2H,m), 7.70-7.90 (2H,m), 8.00-8.10 (1H,m), 8.19 (1H,d,J=8.3Hz), 8.25-8.35 (2H,m), 8.40-8.50 (3H,m), 9.00 (2H,d,J=5.9Hz).

5 MS (FAB) m/z: 538 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 540 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-275] 2-cis,6-Bis(methoxycarbonylmethyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

10 In the same manner as in Example A-105, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.70-2.85 (3H,m), 2.95-3.15 (3H,m), 3.65-3.75 (1H,m), 3.67 (3H,s), 3.75 (3H,s), 4.02 (1H,d,J=12.7Hz), 4.29 (1H,d,J=9.8Hz), 5.25-5.35 (1H,m), 7.45-7.55 (3H,m), 7.75-7.90 (3H,m), 8.75-8.85 (2H,m), 8.98 (2H,s).

15 MS (FAB) m/z: 644 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 646 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-276] 2-[(tert-Butyldiphenylsilyloxy)methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

20 In the same manner as in Example A-105, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.95 (9H x 0.5,s), 1.04 (9H x 0.5,s), 2.50-3.60 (4H,m), 3.70-3.90 (2H,m), 3.95-4.10 (2H,m), 4.45-5.00 (1H,m), 7.30-7.55 (7H,m), 7.55-7.65 (2H,m), 7.70-7.75 (2H,m), 8.05-8.15 (2H,m), 8.25-8.40 (3H,m), 8.95-9.05 (2H,m), 9.25-9.35 (1H,m), 9.40-9.45 (1H,m).

25

MS (FAB) m/z: 768 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 770 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-277] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(hydroxymethyl)-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

5 In the same manner as in Example A-274, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.40-2.70 (2H,m), 3.10-4.00 (6H,m), 4.45-4.75 (1H,m), 7.55-7.65 (1H,m), 8.05-8.15 (2H,m), 8.35 (1H,s), 8.40-8.45 (2H,m), 9.03 (2H,d,J=4.4Hz), 9.46 (2H,s).

10 MS (FAB) m/z: 530 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 532 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-278] 2,cis-6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride

15 In the same manner as in Example A-264, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.40-3.80 (7H,m), 2.74 (3H,s), 2.87 (3H,s), 2.98 (3H,s), 3.05 (3H,s), 3.83 (1H,d,J=12Hz), 4.00-4.05 (1H,m), 5.06 (1H,d,J=8.7Hz),

20 7.58 (1H,dd,J=8.8,2.0Hz), 8.07 (1H,d,J=8.8Hz), 8.10-8.20 (3H,m), 8.35 (1H,s), 8.87 (2H,d,J=5.4Hz), 9.39 (2H,s).

MS (FAB) m/z: 670 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 672 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-279] 4-[2-[[2,cis-6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine

25



## N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.40-3.10 (4H,m), 2.74 (3H,s),  
 2.87 (3H,s), 3.04 (3H,s), 3.33 (3H,s), 3.40-3.50 (2H,m),  
 3.52 (1H,d,J=11.7Hz), 3.82 (1H,d,J=12.7Hz),  
 4.03 (1H,d,J=6.8Hz), 5.05 (1H,d,J=10.3Hz),  
 7.59 (1H,dd,J=8.8,2.0Hz), 7.99 (2H,d,J=7.3Hz),  
 8.07 (1H,d,J=8.3Hz), 8.12 (1H,s), 8.30-8.40 (3H,m),  
 9.30 (2H,s).

MS (FAB) m/z: 686 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 688 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-280] 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(hydroxymethyl)piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.40-2.70 (2H,m), 3.10-4.00 (6H,m),  
 4.47 (1H,d,J=13.7Hz), 4.67 (1H,br s), 4.89 (1H,t,J=5.4Hz),  
 5.16 (1H,t,J=5.4Hz), 7.55-7.65 (1H,m), 7.90-8.00 (2H,m), 8.05-  
 8.15 (2H,m), 8.30-8.40 (3H,m), 9.30 (2H,s).

MS (FAB) m/z: 546 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 548 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-281] 2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-4-[[6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

In the same manner as in Example A-105, the title

compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 0.79, 1.02 (9H, each s), 1.70-5.10 (11H, m), 7.35-7.70 (12H, m), 8.05-8.40 (4H, m), 8.90-9.05 (2H, m), 9.35, 9.45 (2H, each s).

5 MS (FAB)  $m/z$ : 782  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 784  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-282] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-hydroxyethyl)-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine hydrochloride

10 In the same manner as in Example A-274, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.80-2.00 (2H, m), 2.40-3.90 (9H, m), 4.45-5.00 (1H, m), 7.55-7.65 (1H, m), 8.05-8.15 (2H, m), 8.35-8.45 (3H, m), 9.01 (2H, d,  $J=7.8\text{Hz}$ ), 9.45 (2H, d,  $J=2.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 544  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 546  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

15 [Example A-283] 2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-2-yl)pyrimidin-2-yl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

20  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 0.82, 1.09 (9H, each s), 2.05-2.20 (2H, m), 2.55-2.80 (2H, m), 3.15-4.25 (6H, m), 4.70-5.30 (1H, m), 7.10-7.55 (11H, m), 7.70-7.90 (6H, m), 8.70-8.80 (1H, m), 9.22, 9.34 (2H, each s).

MS (FAB)  $m/z$ : 782  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 784  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

25 [Example A-284] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-

2-(2-hydroxyethyl)-1-[5-(pyridin-2-yl)pyrimidin-2-yl]piperazine hydrochloride

In the same manner as in Example A-274, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.80-2.00 (2H,m), 2.40-3.90 (9H,m), 4.45-5.00 (1H,m), 7.50-7.65 (2H,m), 8.00-8.15 (3H,m), 8.15-8.25 (1H,m), 8.34 (1H,s), 8.77 (1H,d,J=4.4Hz), 9.48 (2H,s).  
MS (FAB) m/z: 544  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 546  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-285] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
10 2-[(methoxycarbonyl)methyl]-1-[5-(pyridin-2-yl)pyrimidin-2-yl]piperazine

In the same manner as in Example A-182, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.60-3.30 (5H,m), 3.50-5.45 (7H,m), 7.20-  
15 7.55 (2H,m), 7.70-7.90 (5H,m), 8.76 (1H,d,J=4.9Hz), 8.76 (2H,d,J=2.4Hz).  
MS (FAB) m/z: 572  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 574  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example A-286] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(methoxycarbonyl)methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide  
20

In the same manner as in Example A-6, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.60-3.30 (4H,m), 3.50-5.40 (5H,m), 3.67, 3.74 (3H,each s), 7.30-7.55 (4H,m), 7.70-7.90 (3H,m), 8.30-  
25 8.40 (1H,m), 9.29 (2H,d,J=12.2Hz).

MS (FAB) m/z: 572 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 574 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-287] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

5 In the same manner as in Example A-267, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.30-2.80 (3H,m), 2.74 (3H,s),  
2.85 (3H,s), 2.92 (3H,s), 3.01 (3H,s), 3.10-4.15 (5H,m), 4.50-  
5.15 (1H,m), 7.45-7.65 (3H,m), 7.85-7.95 (1H,m), 8.05-  
10 8.15 (2H,m), 8.34 (1H,s), 8.40-8.45 (1H,m), 9.35 (2H,s).

MS (FAB) m/z: 601 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 603 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-288] 2-[2-[[2-(2-tert-  
Butyldiphenylsilyloxyethyl)-4-[(6-chlorobenzo[b]thien-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine  
15 N-oxide

In the same manner as in Example A-6, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.80-1.10 (9H,m), 2.00-2.20 (2H,m), 2.50-  
2.80 (2H,m), 3.10-4.30 (6H,m), 4.65-5.30 (1H,m), 7.05-  
20 7.90 (17H,m), 8.30-8.40 (1H,m), 9.10-9.30 (2H,m).

MS (FAB) m/z: 798 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 800 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-289] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-  
yl)sulfonyl]-2-(2-hydroxyethyl)piperazin-1-  
yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

25 In the same manner as in Example A-274, the title

compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.80-2.05(1H,m), 2.25-2.45(1H,m), 2.60-2.95(2H,m), 3.00-4.20(7H,m), 4.70-5.10(1H,m), 7.40-7.55(4H,m), 7.70-7.90(3H,m), 8.30-8.40(1H,m), 9.30(2H,s).

5 MS (FAB) m/z: 560 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 562 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-290] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(pyrrolidin-1-yl)carbonyl]methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

10 In the same manner as in Example A-267, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.70-1.90(4H,m), 2.30-4.20(12H,m), 4.50-5.20(1H,m), 7.45-7.65(3H,m), 7.85-7.90(1H,m), 8.05-8.15(2H,m), 8.34(1H,s), 8.43(1H,d,J=6.3Hz), 9.35(2H,s).

15 MS (FAB) m/z: 627 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 629 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-291] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

20 In the same manner as in Example A-267, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.30-2.90(5H,m), 3.15-4.25(6H,m), 4.50-5.20(1H,m), 7.45-7.60(3H,m), 7.85-8.00(1H,m), 8.05-8.15(2H,m), 8.34(1H,s), 8.43(1H,d,J=6.3Hz), 9.35(2H,d,J=4.9Hz).

25 MS (FAB) m/z: 587 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 589 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-292] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(thiomorpholin-4-yl)carbonyl]methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

5 In the same manner as in Example A-267, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.50-2.90 (7H,m), 3.10-4.85 (9H,m), 4.45-5.45 (1H,m), 7.35-7.55 (4H,m), 7.75-7.90 (3H,m), 8.30-8.40 (1H,m), 9.30 (2H,d,J=10.5Hz).

10 MS (FAB) m/z: 659 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 661 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-293] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-cyclopropylcarbamoyl)methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

15 In the same manner as in Example A-267, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.50-0.90 (4H,m), 2.60-6.20 (11H,m), 7.35-7.55 (4H,m), 7.70-7.90 (3H,m), 8.30-8.40 (1H,m), 9.25-9.35 (2H,m).

MS (FAB) m/z: 613 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 615 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example A-294] 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonyl]methyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-267, the title compound was obtained.

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.55-2.85 (4H,m), 3.10-5.45 (13H,m), 7.35-

7.55(4H,m), 7.70-7.90(3H,m), 8.30-8.40(1H,m), 9.25-9.35(2H,m).

MS (FAB) m/z: 643 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 645 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-295] 2-[2-[[2-[(N-Benzylcarbamoyl)methyl]-4-  
5 [(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

In the same manner as in Example A-267, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.65-2.85(3H,m), 2.95-5.45(8H,m), 6.10-  
10 6.30(1H,m), 7.25-7.55(9H,m), 7.70-7.90(3H,m), 8.30-8.40(1H,m), 9.25-9.30(2H,m).

MS (FAB) m/z: 663 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 665 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-296] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-methyl-2-(pyridin-4-yl)thiazol-5-yl]piperazine

15 In the same manner as in Example A-4, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.35(3H,s), 3.00-3.15(4H,br), 3.55-3.73(4H,br), 7.01(1H,s), 7.30(1H,dd,J=8.8,2.2Hz),  
7.49(1H,d,J=8.8Hz), 7.765(1H,d,J=2.0Hz),  
20 7.82(2H,d,J=6.2Hz), 8.69(2H,d,J=6.2Hz).

MS (FAB) m/z: 502 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 504 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-297] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]-2-[(pyrrolidin-1-yl)carbonylmethyl]piperazine

25 In the same manner as in Example A-66, the title

compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.85-2.05 (4H,m), 2.50-3.30 (5H,m), 3.40-3.60 (4H,m), 3.81, 3.90, 4.03, 4.23, 4.64, 5.62 (3H, each br d, J=12.5Hz), 5.15-6.21 (1H,m), 6.99 (1H,s), 7.25-7.50 (4H,m), 7.64 (1H,d, J=5.6Hz), 8.60-8.70 (3H,m), 10.38, 10.95 (1H, each s).

FAB-MS m/z: 599 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 601 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-298] 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(pyrrolidin-1-yl)carbonylmethyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-4, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.65-1.90 (4H,m), 2.30-3.50 (9H,m), 3.50-3.88 (2H,m), 4.41, 5.40 (1H, each br d, J=12.5Hz), 5.02-5.95 (1H,m), 7.02 (1H,s), 7.31 (1H,dd, J=8.8, 2.0Hz), 7.48 (1H,d, J=8.8Hz), 7.75-7.83 (3H,m), 8.26 (2H,d, J=7.1Hz), 8.45, 8.49 (1H, each s), 12.42 (1H, br s).

MS (FAB) m/z: 615 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 617 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-299] 2-[(N-Benzylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine

In the same manner as in Example A-66, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.60-3.06 (4H,m), 3.12-3.57 (1H,m), 3.78-3.95 (1H,m), 3.98-4.12 (1H,m), 4.38-4.56 (2H,m), 4.57-



6.01 (2H,m), 6.47, 6.58 (1H, each br s), 6.97 (1H,s), 7.25-7.52 (8H,m), 7.65 (2H,d, J=6.6Hz), 8.64-8.71 (3H,m), 10.24 (1H,s).

FAB-MS m/z: 635 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 637 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example A-300] 4-[2-[[2-(N-Benzylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

In the same manner as in Example A-4, the title compound was obtained.

10 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.30-2.92 (3H,m), 3.20-3.63 (2H,m), 3.65-3.85 (2H,m), 4.15-4.35 (2H,m), 4.41, 5.41 (1H, each br d, J=13.5Hz), 5.15, 5.98 (1H, each br s), 7.02 (1H,s), 7.15-7.33 (6H,m), 7.48 (1H,d, J=8.6Hz), 7.73-7.81 (3H,m), 8.26 (2H,d, J=6.6Hz), 8.38-8.60 (2H,m), 12.41 (1H, br s).

15 MS (FAB) m/z: 651 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 653 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example A-301] 1-[4-[2-(2-Aminoethyl)pyridin-4-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Example A-7, the title compound was obtained.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.08 (4H,s), 3.23 (2H,br), 3.30 (2H,br), 3.45 (2H,br), 3.73 (2H,br), 7.52 (2H,d, J=8.3Hz), 7.74 (1H,dd, J=5.4, 2.0Hz), 7.80-7.87 (5H,m), 8.06 (2H,br), 8.19 (1H,d, J=8.8Hz), 8.25-8.31 (2H,m), 8.51 (1H, br s), 8.69 (1H,d, J=4.4Hz).

25 MS (FAB) m/z: 535 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 537 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{28}H_{27}ClN_4O_3S \cdot 1.85HCl \cdot 1.4H_2O$

Calculated: C, 53.57; H, 5.08; Cl, 16.10; N, 8.93; S, 5.11.

Found: C, 53.39; H, 5.06; Cl, 15.99; N, 8.81; S, 5.08.

[Example A-302] 1-[[5(6)-Chloroimidazol-2-yl]sulfonyl]-4-  
5 [4-(pyridin-4-yl)benzoyl]piperazine hydrochloride

1-[[5(6)-Chlorobenzimidazol-2-yl]sulfonyl]piperazine  
(507 mg), 1-hydroxybenzotriazole (220 mg), N-  
methylmorpholine (480  $\mu$ l) and 1-ethyl-3-(3-  
dimethylaminopropyl)-carbodiimide (309 mg) were  
10 successively added to the mixture of 4-[(pyridin-4-  
yl)benzoic acid (314 mg), dichloromethane (5.0 ml) and N,N-  
dimethylformamide (2.0 ml), stirred at room temperature for  
5 hours. The mixture was diluted with dichloromethane, and  
then divided into two layers by adding a saturated sodium  
15 chloride solution. The organic layer was washed with a  
saturated sodium chloride solution, dried over sodium  
sulfate, and concentrated under reduced pressure. The  
obtained product was purified by chromatography on a silica  
gel column (dichloromethane:methanol = 15:1). After  
20 dichloromethane was removed from the mixture of  
dichloromethane and methanol under reduced pressure, 1-  
[[5(6)-chloroimidazol-2-yl]sulfonyl]-4-[4-(pyridin-4-  
yl)benzoyl]piperazine (396 mg) was obtained as precipitated  
powder by filtration. 140 mg of this obtained compound was  
25 concentrated by adding 1N aqueous hydrochloride in ethanol  
(3 ml) and ethanol (3 ml), and dried, whereby the title

compound (152 mg) was obtained as colorless amorphous.

IR (KBr)  $\text{cm}^{-1}$  1631, 1431, 1365, 1282, 1155.

$^1\text{H}$ -NMR ( $\text{DMSO-d}_6$ )  $\delta$ , 3.30-4.00 (8H, br), 7.43 (1H, d,  $J$  = 8.8, 2.0 Hz), 7.62 (2H, d,  $J$  = 7.8 Hz), 7.75 (1H, d,  $J$  = 8.8 Hz), 7.80 (1H, s), 8.07 (2H, d,  $J$  = 8.8 Hz), 8.38 (2H, d,  $J$  = 5.9 Hz), 8.97 (2H, d,  $J$  = 5.9 Hz).

MS (FAB)  $m/z$  482  $[(M + H)^+, \text{Cl}^{35}]$ , 484  $[(M + H)^+, \text{Cl}^{37}]$ .

[Example A-303] 4-[4-[[5(6)-chlorobenzimidazol-2-yl]sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

Metachloroperbenzoic acid ( $0^\circ\text{C}$ ; 121 mg) was added to the mixture of 1-[[5(6)-chloroimidazol-2-yl]sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine (191 mg) obtained by Example A-302,  $N,N$ -dimethylformamide (5.0 ml) and chloroform (15 ml) at a temperature of  $0^\circ\text{C}$ , and stirred at a temperature of  $0^\circ\text{C}$  for 3 hours, thereto was added dichloromethane (50 ml), followed by stirring at room temperature for 64 hours. The mixture was divided into two layers by adding a small quantity of sodium thiosulfate solution, and saturated sodium chloride solution. The organic layer was washed with a saturated sodium hydrogencarbonate solution and a saturated sodium chloride solution, dried over sodium sulfate, and concentrated under reduced pressure. The obtained product was purified by chromatography on a silica gel column

(dichloromethane:methanol = 20:1). The mixture of

dichloromethane and methanol was concentrated under reduced pressure, filtered and dried to obtain solid. Thus, the title compound (141 mg) was obtained as colorless amorphous.

5 IR (KBr)  $\text{cm}^{-1}$  1645, 1433, 1371, 1248, 1180, 966, 933.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ , 3.30-3.85 (8H, br), 7.41 (1H, dd,  $J = 8.8, 2.0$  Hz), 7.49 (2H, d,  $J = 7.8$  Hz), 7.68-7.83 (2H, br), 7.80 (2H, d,  $J = 6.8$  Hz), 7.83 (2H, d,  $J = 7.8$  Hz), 8.27 (2H, d,  $J = 6.8$  Hz).

10 MS (FAB)  $m/z$  498  $[(M + H)^+, \text{Cl}^{35}]$ , 500  $[(M + H)^+, \text{Cl}^{37}]$ .

[Example B-1] 1-[[ (6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In saturated aqueous hydrochloric acid in ethanol (5  
15 ml), 1-[[ (6RS)-6-(N-tert-butoxycarbonylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (0.22 g) was dissolved, followed by stirring at room temperature for 90 minutes. The residue obtained by distilling off the  
20 solvent under reduced pressure was recrystallized from a mixed solvent of ethanol and diethyl ether, whereby the title compound (0.14 g, 68%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.30-1.50 (1H, m), 1.90-2.10 (2H, m), 2.40-2.60 (1H, m), 2.60-3.00 (5H, m), 3.03 (4H, m), 3.40-3.80 (4H, br),  
25 7.00-7.10 (3H, m), 7.73 (1H, dd,  $J = 8.8, 2.0$  Hz),

7.81 (1H, dd, J=8.8, 1.5 Hz), 8.05 (3H, br), 8.18 (1H, d, J=8.3 Hz),  
8.20-8.30 (2H, m), 8.49 (1H, s).

MS (FAB) m/z: 498 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 500 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·3/2H<sub>2</sub>O

5 Calculated: C, 55.61; H, 5.74; N, 7.48; Cl, 12.63; S, 5.71.

Found: C, 55.64; H, 5.53; N, 7.77; Cl, 12.79; S, 5.76.

[Example B-2] 1-[[ (6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

10 In the same manner as in Example B-1, the title compound was obtained using 1-[[ (6RS)-6-(N-tert-butoxycarbonylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.30-1.50 (1H, m), 2.00-2.10 (2H, m), 2.40-2.60 (1H, m), 2.60-3.00 (7H, m), 3.00-3.20 (2H, m), 3.30-3.50 (2H, m), 3.82 (2H, m), 4.22 (2H, br), 7.00-7.10 (1H, m), 7.25 (2H, s), 7.73 (1H, dd, J=8.8, 2.4 Hz), 7.81 (1H, dd, J=8.8, 1.5 Hz), 8.00-8.40 (6H, m), 8.52 (1H, s),  
20 11.08 (1H, br).

MS (FAB) m/z: 484 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 486 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>30</sub>ClN<sub>3</sub>O<sub>2</sub>S·2HCl

Calculated: C, 56.07; H, 5.79; N, 7.54; Cl, 19.10; S, 5.76.

Found: C, 56.04; H, 5.79; N, 7.52; Cl, 18.95; S, 5.80.

25 [Example B-3] 1-[[ (2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[[[(2RS)-6-(N-tert-butoxycarbonylaminomethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
5 as a starting material.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.30-1.50(1H,m), 2.00-2.20(1H,m), 2.20-2.40(1H,m), 2.40-2.60(1H,m), 2.75(2H,m), 2.90-3.30(7H,m), 3.60-3.70(2H,m), 3.70-4.00(4H,m), 7.04(1H,d,J=7.8Hz), 7.10-10  
7.30(2H,m), 7.74(1H,m), 7.86(1H,d,J=8.8Hz), 8.20-8.50(6H,m), 8.56(1H,s), 10.69(1H,br).

MS (FAB)  $m/z$ : 484 [(M+H) $^+$ , Cl $^{35}$ ], 486 [(M+H) $^+$ , Cl $^{37}$ ].

Elementary analysis for  $\text{C}_{26}\text{H}_{30}\text{ClN}_3\text{O}_2\text{S}\cdot 2\text{HCl}\cdot 1/2\text{H}_2\text{O}$

Calculated: C, 55.18; H, 5.88; N, 7.42; Cl, 18.79; S, 5.66.

15 Found: C, 55.34; H, 5.70; N, 7.31; Cl, 18.76; S, 5.85.

[Example B-4] 1-[[[(2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[[[(2RS)-6-(N-tert-butoxycarbonylaminomethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.  
20

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.55(1H,m), 1.80-1.90(1H,m), 2.60-2.90(4H,m), 2.90-3.10(5H,m), 3.50-3.80(4H,m), 3.90(2H,s),  
25

7.05 (1H, d, J=7.8Hz), 7.10-7.20 (2H, m), 7.71 (1H, d, J=8.8Hz),  
7.82 (1H, d, J=8.3Hz), 8.10-8.40 (6H, m), 8.50 (1H, s).

MS (FAB) m/z: 498 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 500 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>3</sub>S·1.2HCl·0.8H<sub>2</sub>O

5 Calculated: C, 56.15; H, 5.58; N, 7.55; Cl, 14.02; S, 5.76.

Found: C, 55.93; H, 5.22; N, 7.37; Cl, 14.26; S, 5.70.

[Example B-5] 1-[(7-Aminomethylnaphthalen-2-yl)carbonyl]-  
4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
hydrochloride

10 In the same manner as in Example B-1, the title  
compound was obtained using 1-[[7-(N-tert-  
butoxycarbonylaminomethyl)naphthalen-2-yl]carbonyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
material.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.10 (4H, br), 3.30-3.90 (4H, br),  
4.18 (2H, s), 7.46 (1H, d, J=8.8Hz), 7.69 (1H, d, J=8.8Hz),  
7.73 (1H, d, J=8.8Hz), 7.83 (1H, d, J=8.8Hz), 7.89 (1H, s), 7.90-  
8.00 (3H, m), 8.19 (1H, d, J=8.8Hz), 8.20-8.30 (2H, m), 8.50 (4H, br  
s).

20 MS (FAB) m/z: 494 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 496 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·3/4H<sub>2</sub>O

Calculated: C, 57.41; H, 4.91; N, 7.72; Cl, 13.03; S, 5.89.

Found: C, 57.40; H, 4.87; N, 7.71; Cl, 13.09; S, 5.89.

[Example B-6] 1-[(7-Aminomethylnaphthalen-2-yl)methyl]-4-  
25 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title

compound was obtained using 1-[[7-(N-tert-butoxycarbonylaminomethyl)naphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.92 (2H,m), 3.22 (2H,m), 3.83 (2H,m), 4.20 (2H,d,J=5.4Hz), 4.51 (2H,br), 7.60-7.90 (4H,m), 7.90-8.40 (7H,m), 8.52 (1H,s), 8.57 (3H,br), 11.52 (1H,br).  
MS (FAB)  $m/z$ : 480  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 482  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{26}\text{H}_{26}\text{ClN}_3\text{O}_2\text{S}\cdot 2\text{HCl}\cdot 1/4\text{H}_2\text{O}$

10 Calculated: C, 56.02; H, 5.15; N, 7.54; Cl, 19.08; S, 5.75.  
Found: C, 55.88; H, 5.45; N, 7.34; Cl, 18.90; S, 5.69.

[Example B-7] 1-[(6-Aminomethylnaphthalen-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

15 In tetrahydrofuran (5 ml), 2-(N-tert-butoxycarbonylaminomethyl)-6-methoxycarbonylnaphthalene (0.15 g) was dissolved, followed by the addition of 1N sodium hydroxide (0.70 ml). The resulting mixture was stirred at room temperature for 16 hours. After the  
20 reaction mixture was concentrated under reduced pressure, the concentrate was diluted with dichloromethane and added with dilute hydrochloric acid to separate the organic layer. The organic layer thus obtained was dried over anhydrous sodium sulfate. The residue obtained by  
25 distilling off the solvent under reduced pressure was dissolved in N,N-dimethylformamide (5 ml), followed by the



addition of 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (0.21 g), N-methylmorpholine (54.0  $\mu$ l), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (94.0 mg) and 1-hydroxybenzotriazole (77.0 mg). The resulting mixture was stirred at room temperature for 21 hours. The reaction mixture was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), followed by the reaction in the same manner as in Example B-1, whereby the title compound (77.0 g, 29%) was obtained as colorless crystals.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.09(4H,br), 3.40-3.90(4H,br), 4.19(2H,s), 7.47(1H,d,J=8.3Hz), 7.66(1H,d,J=8.3Hz), 7.73(1H,d,J=9.3Hz), 7.83(1H,d,J=8.8Hz), 7.90-8.10(4H,m), 8.19(1H,d,J=8.8Hz), 8.20-8.30(2H,m), 8.40-8.60(4H,m).  
MS (FAB) m/z: 494 [(M+H) $^+$ , Cl $^{35}$ ], 496 [(M+H) $^+$ , Cl $^{37}$ ].

Elementary analysis for  $\text{C}_{26}\text{H}_{24}\text{ClN}_3\text{O}_3\text{S}\cdot\text{HCl}\cdot\frac{3}{4}\text{H}_2\text{O}\cdot\frac{1}{5}\text{Et}_2\text{O}$

Calculated: C, 57.60; H, 5.14; N, 7.52; Cl, 12.69; S, 5.74.

Found: C, 57.64; H, 5.10; N, 7.12; Cl, 12.69; S, 5.82.

[Example B-8] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(isoquinolin-7-yl)carbonyl]piperazine hydrochloride

In 4N hydrochloric acid, methyl 7-

isoquinolinecarboxylate (J. Org. Chem., 38(21), 3701, 1973) (206 mg) was dissolved, followed by heating under reflux for 4 hours. In the same manner as in Example B-7, a reaction was effected using the residue obtained by distilling off the solvent under reduced pressure and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound (298 mg, 62%) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.95-3.25(4H,m), 3.40-3.60(2H,m), 3.70-3.90(2H,m), 7.73(1H,dd,J=8.8,2.0Hz), 7.84(1H,d,J=8.8Hz), 8.05(1H,d,J=7.3Hz), 8.20(1H,d,J=8.8Hz), 8.25-8.35(3H,m), 8.41(1H,d,J=6.4Hz), 8.45(1H,s), 8.52(1H,s), 8.71(1H,d,J=6.4Hz), 9.79(1H,s).

MS (FAB) m/z: 465 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 467 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>3</sub>S·HCl·2.2H<sub>2</sub>O

Calculated: C, 53.18; H, 4.72; N, 7.75; Cl, 13.08; S, 5.92.

Found: C, 53.11; H, 4.70; N, 7.60; Cl, 13.01; S, 6.16.

[Example B-9] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(quinolyl-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-7, the title compound was obtained using quinoline-2-carboxylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.05(2H,m), 3.17(2H,m), 3.62(2H,m), 3.83(2H,m), 7.61(1H,d,J=8.3Hz), 7.60-7.80(2H,m), 7.80-

7.90 (2H,m), 7.95 (1H,d,J=8.3Hz), 8.00 (1H,d,J=7.3Hz),  
 8.18 (1H,d,J=8.8Hz), 8.20-8.40 (2H,m), 8.43 (1H,d,J=8.3Hz),  
 8.51 (1H,s).

Elementary analysis for  $C_{24}H_{20}ClN_3O_3S$

5 Calculated: C, 61.87; H, 4.33; N, 9.02; Cl, 7.61; S, 6.88.

Found: C, 61.76; H, 4.20; N, 8.73; Cl, 7.65; S, 6.99.

[Example B-10] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
 [(4-hydroxyquinolin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-7, the title  
 compound was obtained using 4-hydroxyquinoline-2-  
 carboxylic acid and 1-[(6-chloronaphthalen-2-  
 yl)sulfonyl]piperazine hydrochloride as starting materials.

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.00-3.30 (4H,br), 3.53 (2H,br),  
 3.77 (2H,br), 6.45 (1H,s), 7.48 (1H,t,J=7.3Hz), 7.70-  
 15 7.90 (4H,m), 8.10-8.40 (4H,m), 8.52 (1H,s).

MS (FAB)  $m/z$ : 482  $[(M+H)^+, Cl^{35}]$ , 484  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{24}H_{20}ClN_3O_4S \cdot 9/10HCl \cdot 1/3CH_3OH$ ,  
 3/2H<sub>2</sub>O

Calculated: C, 52.90; H, 4.60; N, 7.61; Cl, 12.19; S, 5.80.

20 Found: C, 53.17; H, 4.59; N, 7.39; Cl, 12.31; S, 6.07.

[Example B-11] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
 [(8-hydroxyquinolin-7-yl)carbonyl]piperazine hydrochloride

25 In the same manner as in Example B-7, the title  
 compound was obtained using 8-hydroxyquinoline-7-  
 carboxylic acid and 1-[(6-chloronaphthalen-2-  
 yl)sulfonyl]piperazine hydrochloride as starting materials.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.90-3.30 (4H, br), 3.35 (2H, br),  
 3.79 (2H, br), 7.39 (1H, d,  $J=8.3\text{Hz}$ ), 7.53 (1H, d,  $J=8.3\text{Hz}$ ), 7.60-  
 7.90 (3H, m), 8.10-8.40 (3H, m), 8.50 (1H, s),  
 8.60 (1H, d,  $J=7.8\text{Hz}$ ), 8.96 (1H, d,  $J=4.4\text{Hz}$ ).

5 MS (FAB)  $m/z$ : 482  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 484  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{24}\text{H}_{20}\text{ClN}_3\text{O}_4\text{S}\cdot\text{HCl}\cdot\text{CH}_3\text{OH}\cdot 1/4\text{H}_2\text{O}$

Calculated: C, 54.11; H, 4.63; N, 7.57; Cl, 12.78; S, 5.78.

Found: C, 54.40; H, 4.84; N, 7.66; Cl, 13.04; S, 5.99.

10 [Example B-12] 1-[(Benzimidazol-5-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride

In the same manner as in Example B-7, the title compound was obtained using methyl N-triphenylmethyl-5-benzimidazolecarboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

15  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.08 (4H, br), 3.30-4.00 (4H, br),  
 7.48 (1H, d,  $J=8.3\text{Hz}$ ), 7.60-7.90 (4H, m), 8.10-8.30 (3H, m),  
 8.50 (1H, s), 9.51 (1H, s).

MS (FAB)  $m/z$ : 455  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 457  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{22}\text{H}_{19}\text{ClN}_4\text{O}_3\text{S}\cdot\text{HCl}\cdot 5/4\text{H}_2\text{O}$

20 Calculated: C, 51.42; H, 4.41; N, 10.90; Cl, 13.80; S, 6.24.

Found: C, 51.53; H, 4.40; N, 10.71; Cl, 13.61; S, 6.40.

25 [Example B-13] 1-[(Benzimidazol-5-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

In the same manner as in Example B-12, the title compound was obtained using methyl N-triphenylmethyl-5-benzimidazolecarboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride as starting materials.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.67(1H,m), 1.93(1H,m), 3.20-3.90(8H,m), 7.44(1/2H,m), 7.54(1/2H,m), 7.68(1H,m), 7.80-8.00(3H,m), 8.10-8.30(3H,m), 8.49(1/2H,s), 8.55(1/2H,s), 9.56 and 9.57(1H,each s).

MS (FAB) m/z: 469 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 471 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>23</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>3</sub>S·HCl·0.3CH<sub>3</sub>OH·H<sub>2</sub>O

Calculated: C, 52.50; H, 4.76; N, 10.51; Cl, 13.30; S, 6.01.

Found: C, 52.31; H, 4.66; N, 10.50; Cl, 13.34; S,

6.01.

[Example B-14] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-7, the title compound was obtained using sodium thiazolo[5,4-c]pyridine-2-carboxylate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.10-3.30(4H,m), 3.84(2H,m), 4.32(2H,m), 7.69(1H,dd,J=8.8,2.0Hz), 7.83(1H,dd,J=8.8,2.0Hz), 8.10-8.30(4H,m), 8.51(1H,s),

8.79(1H,d,J=5.9Hz), 9.62(1H,s).

MS (FAB) m/z: 473 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 475 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>21</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>3</sub>S<sub>2</sub>·HCl

Calculated: C, 49.51; H, 3.56; N, 11.00; Cl, 13.92; S,  
5 12.59.

Found: C, 49.45; H, 3.71; N, 11.20; Cl, 13.67; S,  
12.55.

[Example B-15] 1-[(E)-4-Chlorostyrylsulfonyl]-4-  
[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
10 hydrochloride

In the same manner as in Example B-7, the title  
compound was obtained using sodium thiazolo[5,4-c]pyridine-  
2-carboxylate and 1-[(E)-4-chlorostyrylsulfonyl]piperazine  
hydrochloride as starting materials.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.30(4H,m), 3.87(2H,m), 4.35(2H,m),  
7.35(1H,d,J=15.6Hz), 7.40-7.50(3H,m), 7.79(1H,d,J=8.3Hz),  
8.22(1H,d,J=5.9Hz), 8.77(1H,d,J=5.9Hz), 9.59(1H,s).

MS (FAB) m/z: 449 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 451 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>19</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>3</sub>S<sub>2</sub>·1/2HCl

20 Calculated: C, 48.85; H, 3.78; N, 11.99; Cl, 11.38; S,  
13.73.

Found: C, 49.18; H, 3.80; N, 12.20; Cl, 11.05; S,  
13.84.

[Example B-16] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
25 [(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
yl)methyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.82-2.88 (4H,m), 2.91-2.99 (4H,m), 3.28-3.36 (2H,m), 3.47-3.55 (4H,m), 4.02 (2H,br s), 6.58 (1H,s), 7.71 (1H,dd,J=8.8,2.0Hz), 7.81 (1H,dd,J=8.8,2.0Hz), 7.23-7.28 (3H,m), 8.49 (1H,s), 9.42 (2H,br s).

MS (FAB) m/z: 462 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 464 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-17] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[trans-3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[trans-3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.95-3.10 (6H,m), 3.32-3.51 (3H,m), 3.60-3.80 (3H,m), 4.12 (2H,s), 6.75 (1H,d,J=15.1Hz), 7.19 (1H,s), 7.50 (1H,d,J=15.1Hz), 7.70 (1H,dd,J=8.8,2.4Hz), 7.81 (1H,dd,J=8.8,2.0Hz), 8.15 (1H,d,J=8.8Hz), 8.22 (1H,d,J=2.0Hz), 8.50 (1H,s), 9.53 (2H,br s).

MS (FAB) m/z: 502 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 504 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>3</sub>S<sub>2</sub>·HCl·0.5H<sub>2</sub>O

Calculated: C, 52.65; H, 4.79; Cl, 12.95; N, 7.67; S, 11.71.

Found: C, 52.36; H, 4.88; Cl, 12.63; N, 8.01; S, 11.39.

5 [Example B-18] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[3-(5-tert-butoxycarbonyl-  
10 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.80-3.60 (16H,m), 4.12 (2H,br s),  
7.11 (1H,br s), 7.74 (1H,dd,J=8.8,2.0Hz),  
15 7.83 (1H,dd,J=8.8,2.0Hz), 8.20 (1H,s), 8.25-8.30 (2H,m),  
8.53 (1H,s), 9.67 (2H,br s).

MS (FAB) m/z: 504 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 506 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>3</sub>S<sub>2</sub>·1.2HCl·1.3H<sub>2</sub>O

Calculated: C, 50.46; H, 5.26; Cl, 13.65; N, 7.36.

20 Found: C, 50.83; H, 5.26; Cl, 13.43; N, 6.97.

[Example B-19] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]piperazine hydrochloride

In the same manner as in Example B-1, the title  
25 compound was obtained using 1-[3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]-4-[(6-



chloronaphthalen-2-yl)sulfonyl]piperazine  
as a starting material.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.90-2.07 (2H,m), 2.72-2.80 (2H,m), 2.82-  
3.21 (8H,m), 3.35 (2H,br s), 3.51 (2H,d,J=11.5Hz),  
5 3.82 (2H,d,J=11.5Hz), 4.06 (2H,s), 6.66 (1H,s),  
7.74 (1H,dd,J=8.8,1.5Hz), 7.85 (1H,dd,J=8.8,1.5Hz),  
8.20 (1H,d,J=8.8Hz), 8.25-8.39 (2H,m), 8.55 (1H,s), 9.50 (2H,br  
s), 11.26 (1H,br s).

MS (FAB)  $m/z$ : 490  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 492  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 Elementary analysis for  $\text{C}_{24}\text{H}_{28}\text{ClN}_3\text{O}_2\text{S}_2 \cdot 2\text{HCl} \cdot 1.6\text{H}_2\text{O}$

Calculated: C, 48.71; H, 5.65; Cl, 17.97; N, 7.10; S,  
10.84.

Found: C, 49.01; H, 5.77; Cl, 17.62; N, 6.96; S,  
10.82.

15 [Example B-20] 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[N-  
[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
yl)methyl]carbamoyl]piperazine hydrochloride

In the same manner as in Example B-1, the title  
compound was obtained using 1-[N-[(5-tert-butoxycarbonyl-  
20 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
yl)methyl]carbamoyl]-4-[(6-chloronaphthalen-2-  
yl)sulfonyl]piperazine as a starting material.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.78-2.86 (2H,br s), 2.88-2.94 (4H,m),  
3.29-3.35 (2H,m), 3.37-3.42 (4H,m), 4.03 (2H,br s),  
25 4.19 (2H,d,J=5.4Hz), 6.62 (1H,s), 7.25 (1H,t,J=5.4Hz),

7.72 (1H, dd, J=8.8, 2.0Hz), 7.82 (1H, dd, J=8.8, 2.0Hz),  
8.16 (1H, d, J=8.8Hz), 8.22-8.26 (2H, m), 8.50 (1H, s), 9.27 (2H, br  
s).

Elementary analysis for  $C_{23}H_{25}ClN_4O_3S_2 \cdot HCl \cdot 1.3H_2O$

5 Calculated: C, 48.90; H, 5.10; Cl, 12.55; N, 9.92.

Found: C, 49.02; H, 5.20; Cl, 12.50; N, 9.76.

[Example B-21] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-1, the title  
compound was obtained using 1-[(5-tert-butoxycarbonyl-  
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-  
[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
material.

15  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.99-3.05 (2H, m), 3.08 (4H, t, J=4.6Hz),  
3.35-3.40 (2H, m), 3.71 (4H, t, J=4.6Hz), 4.11 (2H, s),  
7.17 (1H, s), 7.71 (1H, dd, J=8.8, 2.0Hz),  
7.82 (1H, dd, J=8.8, 2.0Hz), 8.22-8.28 (3H, m), 8.50 (1H, s),  
9.38 (2H, br s).

20 MS (FAB) m/z: 476  $[(M+H)^+, Cl^{35}]$ , 478  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{22}H_{23}ClN_3O_3S_2 \cdot HCl \cdot 3/2H_2O$

Calculated: C, 48.98; H, 4.86; Cl, 13.14; N, 7.79; S,  
11.89.

Found: C, 48.96; H, 4.67; Cl, 13.21; N, 7.74; S,

25 11.93.

[Example B-22] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-

ethoxycarbonyl-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine as a starting material.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.22 (3H, t,  $J=7.0\text{Hz}$ ), 2.38-2.58 (1H, m), 2.65-2.72 (1H, m), 3.04 (2H, br s), 3.29-3.43 (3H, m), 3.70 (1H, br s), 4.01-4.30 (6H, m), 5.18 (1H, br s), 7.27 (1H, s), 7.73 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.82 (1H, d,  $J=8.8\text{Hz}$ ), 8.26 (1H, s), 8.29 (1H, s), 8.54 (1H, s), 9.59 (2H, br s).

MS (FAB)  $m/z$ : 548  $[(M+H)^+, \text{Cl}^{35}]$ , 550  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{25}\text{H}_{26}\text{N}_3\text{ClO}_5\text{S}_2 \cdot 1.2\text{HCl} \cdot 0.6\text{H}_2\text{O}$

Calculated: C, 49.83; H, 4.75; Cl, 12.94; N, 6.97; S, 10.64.

Found: C, 49.62; H, 4.71; Cl, 13.30; N, 7.19; S, 10.56.

[Example B-23] 2-Carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In tetrahydrofuran (1 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonyl-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (95 mg) was dissolved, followed by the addition of ethanol (2 ml) and 1N sodium hydroxide (3 ml).

The resulting mixture was heated under reflux for 30 minutes. To the reaction mixture, 4N hydrochloric acid (2 ml) was added and the precipitate thus obtained was collected by filtration, whereby the title compound (83 mg, 90%) was obtained as a colorless foam.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.30-2.53 (1H,m), 2.58-2.69 (1H,m), 3.04 (2H,br s), 3.29-3.83 (4H,m), 4.07-4.32 (4H,m), 4.90-5.20 (1H,m), 7.03-7.30 (1H,m), 7.71 (1H,dd,  $J=8.8, 2.4\text{Hz}$ ), 7.81 (1H,d,  $J=8.8\text{Hz}$ ), 8.81 (1H,d,  $J=8.8\text{Hz}$ ), 8.20-8.29 (2H,m), 8.52 (1H,s), 9.58 (2H,br s).

MS (FAB)  $m/z$ : 520  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 522  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{23}\text{H}_{22}\text{N}_3\text{ClO}_5\text{S}_2 \cdot 1.2\text{HCl} \cdot 0.8\text{H}_2\text{O}$

Calculated: C, 47.78; H, 4.32; Cl, 13.49; N, 7.27; S, 11.09.

Found: C, 47.41; H, 4.36; Cl, 13.81; N, 7.14; S, 11.01.

[Example B-24] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine

To methanol (4 ml), a solution of 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyano-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine (41 mg) in dichloromethane (1 ml) was added, followed by the addition of hydroxylamine hydrochloride (28 mg) and triethylamine (0.55 ml). The resulting mixture was stirred at room temperature for 2 hours. The residue obtained by

concentrating the reaction mixture under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:3), whereby the title compound (14 mg, 32%) was obtained.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.74-2.79(2H,m), 3.06(4H,s), 3.35-3.38(2H,m), 3.71(4H,s), 4.07(2H,s), 5.32(2H,s), 7.08(1H,s), 7.71(1H,dd,J=8.8,1.6Hz), 7.81(1H,dd,J=8.8,1.6Hz), 8.16(1H,s), 8.23-8.25(2H,m), 8.33(1H,br s), 8.49(1H,s).  
MS (FAB)  $m/z$ : 534  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 536  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 [Example B-25] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]-4-  
15 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.83(2H;br s), 2.99(4H;br s), 3.30(2H;br s), 3.54(4H;br s), 4.00(2H,s), 6.33(1H,s),  
20 7.70(1H,dd,J=8.8,2.0Hz), 7.82(1H,d,J=8.8Hz), 8.16(1H,d,J=8.8Hz), 8.22(1H,s), 8.26(1H,d,J=8.8Hz), 8.50(1H,s), 9.18(2H;br s), 9.82(1H,s).  
MS (FAB)  $m/z$ : 491  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 493  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{22}\text{H}_{23}\text{N}_4\text{ClO}_3\text{S}_2 \cdot \text{HCl} \cdot 0.3\text{H}_2\text{O}$   
25 Calculated: C, 49.59; H, 4.65; Cl, 13.31; N, 10.51; S,

12.03.

Found: C, 49.32; H, 4.63; Cl, 13.34; N, 10.81; S,

12.03.

[Example B-26] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-methyl-N-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using 1-[N-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-N-methylcarbamoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.83(2H,d,J=5.4Hz), 2.97(4H,br s), 3.10(3H,s), 3.28-3.41(6H,m), 4.00(2H,s), 6.35(1H,s), 7.72(1H,dd,J=8.8,2.0Hz), 7.81(1H,dd,J=8.8,2.0Hz), 8.17(1H,d,J=8.8Hz), 8.23-8.31(2H,m), 8.50(1H,s), 9.28(2H,br s).

MS (FAB) m/z: 505 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 507 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>23</sub>H<sub>25</sub>N<sub>4</sub>ClO<sub>3</sub>S<sub>2</sub>·1.1HCl·0.5H<sub>2</sub>O

Calculated: C, 49.85; H, 4.93; Cl, 13.43; N, 10.11; S,

11.57.

Found: C, 49.55; H, 4.92; Cl, 13.23; N, 10.13; S,

11.83.

[Example B-27] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(1-pyrrolin-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

In N,N-dimethylformamide (20 ml), 1-[(6-

chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (400 mg) was dissolved, followed by the addition of triethylamine (0.16 ml) and 2-methoxypyrroline  
 5 (464 mg). The resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure. To the residue, 1N hydrochloric acid was added and the precipitate thus formed was collected by filtration, whereby the title compound  
 10 (411 mg, 88%) was obtained as a pale yellow foamy solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.07-2.18 (2H,m), 2.90-3.11 (8H,m), 3.62 (2H,t,J=6.8Hz), 3.72 (4H,br), 3.80 (2H,t,J=5.9Hz), 3.99 (2H,t,J=5.9Hz), 4.62 (1H,br s), 4.73 (1H,br s), 7.10 (1H,s), 7.50 (1H,s), 7.72 (1H,dd,J=8.8,2.0Hz),  
 15 7.82 (1H,dd,J=8.8,2.0Hz), 8.18 (1H,d,J=8.8Hz), 8.22-8.28 (2H,m), 8.51 (1H,s), 10.37 (1H,br s), 10.53 (1H,br s).

MS (FAB) m/z: 542 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 544 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub>S<sub>2</sub>·1.3HCl·0.4H<sub>2</sub>O  
 Calculated: C, 52.25; H, 4.91; Cl, 13.64; N, 9.37; S,  
 20 10.73.

Found: C, 52.34; H, 5.03; Cl, 13.56; N, 9.36; S, 10.74.

[Example B-28] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride  
 25

In the same manner as in Example B-1, the title

compound was obtained using 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.01 (2H, t, J=5.9 Hz), 3.11 (4H, br), 3.44 (2H, br s), 3.74 (2H, br s), 4.32-4.46 (4H, m), 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.83 (1H, dd, J=8.8, 2.0 Hz), 8.15 (1H, d, J=8.8 Hz), 8.23 (1H, s), 8.26 (1H, d, J=8.8 Hz), 8.30 (1H, s).

MS (FAB) m/z: 477 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 479 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>21</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>3</sub>S<sub>2</sub>·HCl·0.2H<sub>2</sub>O

Calculated: C, 48.78; H, 4.37; Cl, 13.71; N, 10.84; S, 12.40.

Found: C, 48.60; H, 4.50; Cl, 13.58; N, 10.62; S,

12.29.

[Example B-29] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride; and 1-[(6-carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In a similar manner to Referential Example 33 and Example B-24 by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a starting material, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-



aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride and also  
 1-[(6-carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine were obtained.

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride:

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.77(2H, br s), 3.09(4H, br),  
 3.48(2H, t,  $J=5.4\text{Hz}$ ), 3.73(2H, br s), 4.30-4.50(4H, m),  
 5.61(1H, br s), 7.71(1H, dd,  $J=8.8\text{Hz}, 2.0\text{Hz}$ ),  
 7.82(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.15(1H, d,  $J=8.8\text{Hz}$ ),  
 8.22(1H, d,  $J=1.5\text{Hz}$ ), 8.25(1H, d,  $J=8.8\text{Hz}$ ), 8.50(1H, s),  
 8.53(1H, br s).

MS (FAB)  $m/z$ : 535  $[(M+H)^+, \text{Cl}^{35}]$ , 537  $[(M+H)^+, \text{Cl}^{37}]$ .

1-[(6-Carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine:

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.75(2H, br s), 3.09(4H, br),  
 3.63(2H, t,  $J=5.9\text{Hz}$ ), 3.73(2H, br s), 4.39(2H, br s),  
 4.59(2H, s), 6.17(2H, s), 7.70(1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
 7.82(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.14(1H, d,  $J=8.8\text{Hz}$ ),  
 8.21(1H, d,  $J=1.5\text{Hz}$ ), 8.25(1H, d,  $J=8.8\text{Hz}$ ), 8.50(1H, s).

MS (FAB)  $m/z$ : 520  $[(M+H)^+, \text{Cl}^{35}]$ , 522  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{22}\text{H}_{22}\text{ClN}_5\text{O}_4\text{S}_2 \cdot \text{H}_2\text{O}$

Calculated: C, 49.11; H, 4.50; N, 13.02.

Found: C, 48.98; H, 4.12; N, 12.83.

[Example B-30] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
 [[6-(1-pyrrolin-2-yl)-4,5,6,7-tetrahydrothiazolo[5,4-  
 5 c]pyridin-2-yl]carbonyl]piperazine hydrochloride

In the same manner as in Example B-27, the title  
 compound was obtained using 1-[(6-chloronaphthalen-2-  
 yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-  
 2-yl)carbonyl]piperazine hydrochloride as a starting  
 10 material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.07-2.15 (2H,m), 2.94-3.16 (8H,m),  
 3.63 (2H,t,J=7.3Hz), 3.75 (2H,br s), 3.90 (2H,br s),  
 4.39 (2H,br s), 4.93 (2H,s), 7.70 (1H,dd,J=8.8,2.0Hz),  
 7.83 (1H,dd,J=8.8,2.0Hz), 8.15 (1H,d,J=8.8Hz),  
 15 8.22 (1H,d,J=2.0Hz), 8.25 (1H,d,J=8.8Hz), 8.50 (1H,s).

MS (FAB) m/z: 544 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 546 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>25</sub>H<sub>26</sub>ClN<sub>5</sub>O<sub>3</sub>S<sub>2</sub>·1.4HCl·CH<sub>3</sub>OH

Calculated: C, 49.79; H, 5.05; Cl, 13.57; N, 11.17; S,  
 10.23.

20 Found: C, 49.44; H, 4.78; Cl, 13.63; N, 10.83; S,  
 10.15.

[Example B-31] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
 [(6-formyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazine

25 In the same manner as in Example B-7, the title  
 compound was obtained using 1-[(6-chloronaphthalen-2-

yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride and formic acid as starting materials.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.74-2.88 (2H,m), 3.10 (4H,br),  
 5 3.31 (2H,s), 3.66-3.86 (4H,m), 4.64-4.73 (2H,m),  
 7.69 (1H,dd,J=8.8,2.0Hz), 7.82 (1H,dd,J=8.8,2.0Hz),  
 8.14 (1H,d,J=8.8Hz), 8.15-8.22 (2H,m), 8.24 (1H,d,J=8.8Hz),  
 8.50 (1H,s).

MS (FAB) m/z: 505 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 507 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 Elementary analysis for C<sub>22</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S<sub>2</sub>·1/5H<sub>2</sub>O

Calculated: C, 51.95; H, 4.24; Cl, 6.97; N, 11.02; S,  
 12.61.

Found: C, 52.18; H, 4.30; Cl, 6.69; N, 10.71; S,  
 12.21.

15 [Example B-32] 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In dichloromethane (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-  
 20 2-yl)carbonyl]piperazine hydrochloride (400 mg) was  
 suspended, followed by the addition of triethylamine (0.22 ml) and acetic acid (0.05 ml). The resulting mixture was  
 stirred at room temperature for 5 minutes. To the reaction  
 mixture, a 30% aqueous solution (0.08 ml) of formaldehyde  
 25 and sodium triacetoxyborohydride (264 mg) were added. The  
 resulting mixture was stirred at room temperature for 10

minutes. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue. The resulting mixture was washed with water and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in a saturated hydrochloride solution in ethanol (1 ml), followed by concentration under reduced pressure. The residue thus obtained was crystallized from hexane and ethyl acetate, whereby the title compound (298 mg, 71%) was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.89(3H,s), 3.10(6H,br), 3.32-3.81(4H,m), 4.30-4.81(4H,m), 7.71(1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.82(1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 8.15(1H,d,  $J=8.8\text{Hz}$ ), 8.20-8.28(2H,m), 8.50(1H,s), 11.28(1H,br s).

MS (FAB)  $m/z$ : 491  $[(M+H)^+, \text{Cl}^{35}]$ , 493  $[(M+H)^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{22}\text{H}_{23}\text{ClN}_4\text{O}_3\text{S}_2 \cdot \text{HCl} \cdot 0.6\text{H}_2\text{O}$

Calculated: C, 49.09; H, 4.72; Cl, 13.17; N, 10.41; S, 11.91.

Found: C, 48.88; H, 4.78; Cl, 13.26; N, 10.42; S, 12.03.

[Example B-33] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridinium iodide

In N,N-dimethylformamide (20 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

hydrochloride (200 mg) was dissolved, followed by the addition of methyl iodide (0.05 ml) and potassium carbonate (79.0 mg). The resulting mixture was stirred overnight at 80°C. The reaction mixture was concentrated under reduced pressure. Water was added to the residue and the precipitate so formed was collected by filtration. The precipitate was dissolved in a 1:1 mixed solution of dichloromethane and methanol. Ethyl acetate was added to the resulting solution and the precipitate thus formed was collected by filtration, whereby the title compound (144 mg, 56%) was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.05-3.23 (12H, m), 3.77 (2H, t,  $J=5.9\text{Hz}$ ), 4.40 (2H, br s), 4.79 (2H, br s), 7.71 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.83 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.15 (1H, d,  $J=8.8\text{Hz}$ ), 8.20-8.27 (2H, m), 8.52 (1H, s).

MS (FD)  $m/z$ : 505 ( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 507 ( $\text{M}^+$ ,  $\text{Cl}^{37}$ ).

Elementary analysis for  $\text{C}_{23}\text{H}_{26}\text{ClIN}_4\text{O}_3\text{S}_2 \cdot 1/2\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$

Calculated: C, 44.35; H, 4.47; N, 8.28.

Found: C, 44.52; H, 4.23; N, 8.01.

[Example B-34] 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine N-oxide

In acetone (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (400 mg) was suspended, followed by the addition of a 1N aqueous

solution (0.38 ml) of sodium hydroxide and a 30% aqueous solution (3.50 ml) of hydrogen peroxide. The resulting mixture was stirred at room temperature for 8 days. After the reaction mixture was concentrated under reduced pressure, the residue was purified by chromatography through a synthetic adsorbent ("Diaion® HP-20", trade name; water ~ water : acetonitrile = 2:5), whereby the title compound (84 mg, 39%) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.83-2.90 (1H,m), 3.10 (5H,br), 3.20-3.47 (4H,m), 3.61-3.83 (3H,m), 4.28-4.50 (3H,m), 4.78-4.85 (1H,m), 7.69 (1H,dd,J=8.8,2.0Hz), 7.82 (1H,dd,J=8.8,2.0Hz), 8.14 (1H,d,J=8.8Hz), 8.19-8.27 (2H,m), 8.50 (1H,s).

MS (FD) m/z: 506 (M<sup>+</sup>, Cl<sup>35</sup>), 508 (M<sup>+</sup>, Cl<sup>37</sup>).

[Example B-35] 2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

To trifluoroacetic acid (1 ml), a solution of 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (303 mg) dissolved in dichloromethane (1 ml) was added, followed by concentration under reduced pressure. The precipitate thus formed was collected by filtration and washed with diethyl ether, whereby the title compound (263 mg, 83%) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.39-2.70 (2H,m), 2.92-3.06 (2H,m), 3.42-3.77 (4H,m), 4.25-4.50 (7/2H,m), 4.97 (1/2H,br s), 5.35-5.44 (1/2H,m), 6.14 (1/2H,br s), 7.30-7.39 (1H,m), 7.66-7.73 (2H,m), 7.77-7.82 (1H,m), 8.16 (1H,d,J=8.8Hz), 8.21-8.28 (2H,m), 8.49 (1H,s), 9.26 (2H,br s).

MS (FAB) m/z: 520 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 522 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>4</sub>S<sub>2</sub>·CF<sub>3</sub>CO<sub>2</sub>H·0.6H<sub>2</sub>O

Calculated: C, 44.29; H, 3.73; Cl, 5.40; F, 9.55; N, 10.67; S, 9.77.

Found: C, 44.59; H, 3.79; Cl, 5.26; F, 9.54; N, 10.28; S, 9.72.

[Example B-36] 2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-32, the title compound was obtained using 2-carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.37-2.70 (2H,m), 2.91 (3H,s), 3.00-3.78 (6H,m), 4.28-4.77 (7/2H,m), 4.97 (1/2H,br s), 5.40-5.50 (1/2H,m), 6.14 (1/2H,br s), 7.32-7.40 (1H,m), 7.68-7.75 (2H,m), 7.77-7.83 (1H,m), 8.15 (1H,d,J=8.8Hz), 8.21-8.28 (2H,m), 8.49 (1H,s).

MS (FAB) m/z: 534 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 536 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{23}H_{24}ClN_5O_4S_2 \cdot HCl \cdot 2.5H_2O$

Calculated: C, 44.88; H, 4.91; Cl, 11.52; N, 11.38; S, 10.42.

Found: C, 44.83; H, 4.89; Cl, 11.65; N, 11.31; S, 10.46.

[Example B-37] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

The crude product, which had been obtained by the reaction in the same manner as in Example B-32 by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (132 mg) and glyoxylic hydrate (82 mg) as starting materials, was suspended in tetrahydrofuran (50 ml). Triethylamine (0.22 ml) and ethyl chloroformate (0.03 ml) were added to the resulting suspension under ice cooling, followed by stirring at room temperature for 15 minutes. To the reaction mixture, sodium borohydride (50 mg) and water (10 ml) were added to the reaction mixture and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane, washed with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica



gel column (dichloromethane ~ dichloromethane : methanol = 100:3), followed by dissolution in saturated hydrochloride in ethanol (1 ml). The resulting solution was then concentrated under reduced pressure. The concentrate was pulverized and washed in ethyl acetate, whereby the title compound (52 mg, 33%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.11(4H, br s), 3.20-3.57(6H, m), 3.69-3.87(4H, m), 4.34-4.82(4H, m), 5.38(1H, br s), 7.71(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.82(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.15(1H, d,  $J=8.8\text{Hz}$ ), 8.22(1H, s), 8.25(1H, d,  $J=8.8\text{Hz}$ ), 8.50(1H, s), 10.48(1H, br s).

MS (FAB)  $m/z$ : 521  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 523  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

In the same manner as in Example B-32, the compounds of Examples B-38, B-39 and B-40 were obtained, respectively by using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a starting material.

[Example B-38] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.07-3.17(6H, m), 3.63(2H, t,  $J=6.3\text{Hz}$ ), 3.74(2H, br s), 4.39(2H, br s), 4.58(2H, s), 4.61(2H, s), 7.50-7.64(1H, m), 7.67-7.73(2H, m), 7.82(1H, dd,  $J=8.8, 1.5\text{Hz}$ ), 7.97(1H, m), 8.15(1H, d,  $J=8.8\text{Hz}$ ), 8.22(1H, d,  $J=1.5\text{Hz}$ ), 8.25(1H, d,  $J=8.8\text{Hz}$ ), 8.50(1H, s), 8.69(1H, d,  $J=4.9\text{Hz}$ ).

MS (FAB)  $m/z$ : 568  $[(M+H)^+, Cl^{35}]$ , 570  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{27}H_{26}ClN_5O_3S_2 \cdot 2HCl \cdot 0.8H_2O$

Calculated: C, 49.48; H, 4.55; Cl, 16.23; N, 10.68; S, 9.78.

5 Found: C, 49.72; H, 4.48; Cl, 16.31; N, 10.86; S, 9.53.

[Example B-39] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
[[6-(pyridin-3-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl]carbonyl]piperazine hydrochloride

10  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.03-3.27(6H,m), 3.40-3.81(4H,m),  
3.74(2H,br s), 4.40(2H,br s), 4.50(2H,s), 4.70(2H,s),  
7.70(1H,dd,J=8.8,2.4Hz), 7.82(1H,d,J=8.8Hz),  
8.15(1H,d,J=8.8Hz), 8.22(1H,s), 8.25(1H,d,J=8.8Hz),  
8.50(1H,s), 8.73(1H,d,J=7.8Hz), 8.93(1H,d,J=4.4Hz).

15 MS (FAB)  $m/z$ : 568  $[(M+H)^+, Cl^{35}]$ , 570  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{27}H_{26}ClN_5O_3S_2 \cdot 2.9HCl \cdot 4.5H_2O$

Calculated: C, 42.96; H, 5.06; Cl, 18.32; N, 9.28.

Found: C, 42.97; H, 4.84; Cl, 18.19; N, 9.23.

[Example B-40] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
20 [[6-(pyridin-4-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl]carbonyl]piperazine hydrochloride

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.11(4H,br s), 3.19(2H,br s),  
3.64(2H,br s), 3.74(2H,br s), 4.41(2H,br s), 4.49(2H,s),  
4.80(2H,s), 7.69(1H,dd,J=8.8,2.0Hz),

25 7.82(1H,dd,J=8.8,2.0Hz), 8.15(1H,d,J=8.8Hz),

8.21 (1H, d, J=2.0Hz), 8.25 (1H, d, J=8.8Hz), 8.41 (2H, d, J=6.3Hz),  
8.50 (1H, s), 9.04 (2H, d, J=6.3Hz).

MS (FAB) m/z: 568 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 570 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>27</sub>H<sub>26</sub>ClN<sub>5</sub>O<sub>3</sub>S<sub>2</sub>·2.7HCl·6.0H<sub>2</sub>O

5 Calculated: C, 41.86; H, 5.30; Cl, 16.93; N, 9.04; S, 8.28.

Found: C, 42.05; H, 4.98; Cl, 16.92; N, 9.37; S, 8.61.

[Example B-41] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-1, the title compound was obtained using 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(E)-4-chlorostyrylsulfonyl]piperazine as a starting material.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.04 (2H, br s), 3.23 (4H, br), 3.47 (2H, br s), 3.77 (2H, br s), 4.35-4.50 (2H, m), 7.33 (1H, d, J=15.6Hz), 7.43 (1H, d, J=15.6Hz), 7.49 (1H, d, J=8.3Hz), 7.79 (1H, d, J=8.3Hz), 9.57 (2H, br s).

MS (FAB) m/z: 453 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 455 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 Elementary analysis for C<sub>19</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>3</sub>S<sub>2</sub>·HCl·0.3H<sub>2</sub>O

Calculated: C, 46.12; H, 4.60; Cl, 14.33; N, 11.32; S, 12.96.

Found: C, 46.42; H, 4.66; Cl, 14.38; N, 11.02; S, 13.02.

25 [Example B-42] 1-[(E)-4-Chlorostyrylsulfonyl]-4-[6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-32, the title compound was obtained using 1-[(E)-4-chlorostyrylsulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.92(3H,s), 3.01-3.32(6H,br), 3.35-3.88(4H,m), 4.29-4.84(4H,m), 7.33(1H,d,J=15.6Hz), 7.49(1H,d,J=15.6Hz), 7.49(1H,d,J=8.3Hz), 7.79(1H,d,J=8.3Hz), 11.31(1H,br s).

MS (FAB) m/z: 467 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 469 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>20</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>3</sub>S<sub>2</sub>·HCl·0.2H<sub>2</sub>O

Calculated: C, 47.37; H, 4.85; Cl, 13.98; N, 11.05; S, 12.65.

Found: C, 47.30; H, 4.92; Cl, 14.05; N, 11.03; S, 12.49.

[Example B-43] (3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]pyrrolidine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using (3S)-1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-3-[(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine as a starting material.

[α]<sub>D</sub> = -69.72° (25°C, c=1.00, CH<sub>3</sub>OH).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> at 100°C) δ: 1.88-1.89(1H,m), 2.10-  
 2.25(1H,m), 3.02-3.07(2H,m), 3.10-3.50(6H,m), 4.02(1H,s),  
 4.12(2H,s), 4.45(2H,s), 7.12(1H,s), 7.65(1H,d,J=8.3Hz),  
 7.91(1H,d,J=8.3Hz), 8.10(1H,d,J=8.3Hz), 8.14(1H,s),  
 5 8.16(1H,d,J=8.3Hz), 8.18(1H,br s), 8.48(1H,s), 9.65(2H,br  
 s).

MS (FD) m/z: 461 (M<sup>+</sup>, Cl<sup>35</sup>), 463 (M<sup>+</sup>, Cl<sup>37</sup>).

Elementary analysis for C<sub>22</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>2</sub>S<sub>2</sub>·2.1HCl·H<sub>2</sub>O

Calculated: C, 47.47; H, 5.09; Cl, 19.74; N, 7.55; S,  
 10 11.52.

Found: C, 47.55; H, 5.13; Cl, 19.85; N, 7.45; S,  
 11.48.

[Example B-44] (3S)-3-[(6-Chloronaphthalen-2-  
 yl)sulfonamido]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-  
 15 2-yl)carbonyl]pyrrolidine hydrochloride

In the same manner as in Example B-1, the title  
 compound was obtained using (3S)-1-[(5-tert-butoxycarbonyl-  
 4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-3-  
 [(6-chloronaphthalen-2-yl)sulfonamido]pyrrolidine as a  
 20 starting material.

[α]<sub>D</sub> = -62.70° (25°C, c=1.00, CH<sub>3</sub>OH).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> at 100°C) δ: 1.82-1.90(1H,m), 1.96-  
 2.05(1H,m), 3.05(2H,t,J=6.0Hz), 3.42-3.57(2H,m), 3.60-  
 3.72(2H,m), 3.84-3.90(1H,m), 4.12(2H,s), 4.45(2H,s),  
 25 7.25(1H,s), 7.64(1H,dd,J=8.3,1.6Hz),

7.90 (1H, dd, J=8.3, 1.6 Hz), 7.97 (1H, d, J=5.6 Hz),  
 8.08 (1H, d, J=8.7 Hz), 8.12 (1H, s), 8.14 (1H, d, J=8.7 Hz),  
 8.47 (1H, s), 9.55 (2H, br s).

MS (FAB) m/z: 476 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 478 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 Elementary analysis for C<sub>22</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S<sub>2</sub>.HCl

Calculated: C, 51.56; H, 4.52; Cl, 13.84; N, 8.20; S,  
 12.51.

Found: C, 51.25; H, 4.61; Cl, 13.68; N, 7.98; S,  
 12.36.

10 [Example B-45] (3S)-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-  
 3-[[ (4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
 yl)methyl]amino]pyrrolidine hydrochloride

In the same manner as in Example B-1, the title  
 compound was obtained using (3S)-3-[[ (5-tert-  
 15 butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
 yl)methyl]amino]-1-[(6-chloronaphthalen-2-  
 yl)sulfonyl]pyrrolidine as a starting material.

[α]<sub>D</sub>=+34.82° (25°C, c=1.00, CH<sub>3</sub>OH).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.98-2.20 (2H, m), 2.99-3.04 (2H, m), 3.19-  
 20 3.26 (1H, m), 3.30-3.50 (3H, m), 3.61-3.72 (1H, m), 3.52-  
 3.60 (1H, m), 4.13 (2H, s), 4.29 (2H, s), 7.09 (1H, s),  
 7.71 (1H, dd, J=8.8, 2.0 Hz), 7.89 (1H, dd, J=8.8, 2.0 Hz),  
 8.17 (1H, d, J=8.8 Hz), 8.25 (1H, d, J=2.0 Hz), 8.30 (1H, s),  
 8.57 (1H, s), 9.55 (2H, br s), 9.7-10.0 (1H, m).

25 MS (FD) m/z: 461 (M<sup>+</sup>, Cl<sup>35</sup>), 463 (M<sup>+</sup>, Cl<sup>37</sup>).

Elementary analysis for  $C_{22}H_{24}ClN_3O_2S_2 \cdot 2HCl \cdot 0.2H_2O$

Calculated: C, 49.06; H, 4.94; Cl, 19.75; N, 7.80; S, 11.91.

Found: C, 48.88; H, 4.97; Cl, 19.65; N, 7.67; S, 11.84.

[Example B-46] (3S)-3-[(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine hydrochloride

In the same manner as in Example B-1, the title compound was obtained using (3S)-3-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine as a starting material.

$[\alpha]_D^{25} = +33.56^\circ$  (25°C,  $c=1.00$ ,  $CH_3OH$ ).

$^1H$ -NMR ( $DMSO-d_6$ )  $\delta$ : 1.85-1.95 (1H,m), 1.95-2.05 (1H,m), 3.04 (2H,m), 3.24-3.40 (1H,m), 3.41-3.53 (3H,m), 4.04-4.24 (3H,m), 7.34 (1H,s), 7.67 (1H,d,  $J=8.8$ Hz), 7.84 (1H,d,  $J=8.8$ Hz), 8.03 (1H,d,  $J=8.8$ Hz), 8.17 (1H,s), 8.22 (1H,d,  $J=8.8$ Hz), 8.27 (1H,d,  $J=5.7$ Hz), 8.50 (1H,s), 9.59 (1H,br s), 9.71 (1H,br s).

MS (FD)  $m/z$ : 476  $[(M+H)^+, Cl^{35}]$ , 478  $[(M+H)^+, Cl^{37}]$ .

[Example B-47] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]homopiperazine hydrochloride

In the same manner as in Example B-1, the title

compound was obtained using 1-[(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine as a starting material.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.83(2H, br s), 3.04(2H, t,  $J=5.4\text{Hz}$ ), 3.30-3.59(6H, m), 3.60-3.88(4H, m), 4.14(2H, s), 7.20(1H, br s), 7.69(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.84(1H, d,  $J=8.8\text{Hz}$ ), 8.10(1H, d,  $J=8.8\text{Hz}$ ), 8.17-8.21(2H, m), 8.50(1H, s), 9.57(2H, br s).

10 MS (FAB)  $m/z$ : 490  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 492  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{23}\text{H}_{25}\text{ClN}_3\text{O}_3\text{S}_2 \cdot 1.1\text{HCl} \cdot 0.2\text{H}_2\text{O}$

Calculated: C, 51.66; H, 4.99; Cl, 13.92; N, 7.86.

Found: C, 51.46; H, 4.61; Cl, 13.55; N, 8.05.

[Example B-48] 4-[(6-Chloronaphthalen-2-yl)sulfonamido]-1-  
15 [(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperidine hydrochloride

In the same manner as in Examples B-7 and B-1, the title compound was obtained using 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-carboxylic acid  
20 (WO94/21599) and 4-[(6-chloronaphthalen-2-yl)sulfonamido]piperidine trifluoroacetate as starting materials.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.26-1.38(2H, m), 1.58-1.65(2H, m), 2.93-3.13(4H, m), 3.29-3.40(3H, m), 3.90-4.05(2H, m), 4.11(2H, s),  
25 7.16(1H, s), 7.68(1H, dd,  $J=8.0, 2.0\text{Hz}$ ),



7.92 (1H, dd, J=8.8, 2.0 Hz), 8.07 (1H, d, J=7.3 Hz),  
 8.13 (2H, d, J=8.8 Hz), 8.20 (1H, d, J=7.3 Hz), 8.23 (1H, s),  
 8.51 (1H, s), 9.71 (2H, br s).

MS (FAB) m/z: 490 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 492 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 Elementary analysis for C<sub>23</sub>H<sub>25</sub>ClN<sub>3</sub>O<sub>3</sub>S<sub>2</sub>·2.4HCl·3H<sub>2</sub>O

Calculated: C, 43.67; H, 5.32; Cl, 19.05; N, 6.64.

Found: C, 43.85; H, 5.10; Cl, 19.07; N, 6.63.

[Example B-49] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[(6-aminohydroxyiminomethylbenzofuran-2-

10 yl)carbonyl]piperazine

In the same manner as in Example B-24, the title compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(6-cyanobenzofuran-2-yl)carbonyl]piperazine as a starting material.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.11 (4H, s), 3.83 (4H, br), 5.90 (2H, br s),

7.34 (1H, s), 7.64-7.75 (3H, m), 7.83 (1H, dd, J=8.8, 2.0 Hz),

7.89 (1H, s), 8.17 (1H, d, J=8.8 Hz), 8.23 (1H, d, J=1.5 Hz),

8.26 (1H, d, J=8.8 Hz), 8.51 (1H, s), 9.77 (1H, s).

MS (FAB) m/z: 513 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 515 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 Elementary analysis for C<sub>24</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>5</sub>S·1/5H<sub>2</sub>O

Calculated: C, 55.80; H, 4.18; Cl, 6.86; N, 10.70; S, 6.21.

Found: C, 55.65; H, 4.25; Cl, 6.81; N, 10.70; S, 6.37.

[Example B-50] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-

[(5-aminohydroxyiminomethylbenzothiophen-2-

25 yl)carbonyl]piperazine

In the same manner as in Example B-24, the title

compound was obtained using 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(5-cyanobenzothiophen-2-yl)carbonyl]piperazine as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.11(4H,s), 3.77(4H,s), 5.87(2H,br s),  
 5 7.67(1H,s), 7.71(1H,d,J=2.0Hz), 7.75(1H,d,J=8.8Hz),  
 7.83(1H,dd,J=8.8,2.0Hz), 7.94(1H,d,J=8.8Hz), 8.15(1H,s),  
 8.17(1H,d,J=8.8Hz), 8.25(1H,d,J=8.8Hz), 8.29(1H,d,J=8.3Hz),  
 8.50(1H,s), 9.68(1H,s).

MS (FAB) m/z: 529 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 531 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 Elementary analysis for C<sub>24</sub>H<sub>21</sub>N<sub>4</sub>ClO<sub>4</sub>S<sub>2</sub>·0.3H<sub>2</sub>O

Calculated: C, 53.94; H, 4.07; N, 10.48.

Found: C, 54.22; H, 4.17; N, 10.23.

[Example B-51] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
 [(1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]piperazine  
 15 hydrochloride

In the same manner as in Example B-1, the title  
 compound was obtained using 1-[(2-tert-butoxycarbonyl-  
 1,2,3,4-tetrahydroisoquinolin-6-yl)carbonyl]-4-[(6-  
 chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
 20 material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.89-3.29(4H,m), 3.20-3.83(8H,m),  
 4.25(2H,s), 7.10-7.25(3H,m), 7.71(1H,d,J=8.3Hz),  
 7.81(1H,d,J=8.3Hz), 8.17(1H,d,J=8.8Hz), 8.15-8.25(2H,m),  
 8.49(1H,s), 9.54(2H,br s).

25 MS (FAB) m/z: 470 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 472 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{24}H_{24}ClN_3O_3S \cdot HCl \cdot 2.0H_2O$

Calculated: C, 53.14; H, 5.39; Cl, 13.07; N, 7.75; S, 5.91.

Found: C, 53.43; H, 5.43; Cl, 13.15; N, 8.07; S, 5.55.

[Example B-52] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-  
 5 [(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-  
 yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-32, the title  
 compound was obtained using 1-[(6-chloronaphthalen-2-  
 yl)sulfonyl]-4-[(1,2,3,4-tetrahydroisoquinolin-6-  
 10 yl)carbonyl]piperazine hydrochloride as a starting  
 material.

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.88 (3H, s), 2.90-3.80 (13H, m), 4.12-  
 4.56 (1H, m), 7.19 (1H, s), 7.20 (2H, d,  $J=6.8$  Hz),  
 7.72 (1H, dd,  $J=8.8, 2.0$  Hz), 7.81 (1H, d,  $J=8.8$  Hz),  
 15 8.17 (1H, d,  $J=8.8$  Hz), 8.24-8.28 (2H, m), 8.49 (1H, s),  
 10.93 (1H, br s).

MS (FAB)  $m/z$ : 484  $[(M+H)^+, Cl^{35}]$ , 486  $[(M+H)^+, Cl^{37}]$ .

Elementary analysis for  $C_{24}H_{24}ClN_3O_3S \cdot HCl \cdot 2.3H_2O$

Calculated: C, 53.44; H, 5.67; Cl, 12.62; N, 7.48; S, 5.71.

20 Found: C, 53.71; H, 5.81; Cl, 12.37; N, 7.26; S, 5.62.

[Example B-53] 6-[[4-[(6-Chloronaphthalen-2-  
 yl)sulfonyl]piperazin-1-yl]carbonyl]-2,2-dimethyl-1,2,3,4-  
 tetrahydroisoquinolinium iodide

In the same manner as in Example B-33, the title  
 25 compound was obtained using 1-[(6-chloronaphthalen-2-  
 yl)sulfonyl]-4-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-

yl)carbonyl]piperazine hydrochloride as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.90-3.85 (18H, m), 4.61 (2H, s),  
7.19 (1H, d, J=7.8 Hz), 7.24 (1H, d, J=7.8 Hz), 7.28 (1H, s),  
5 7.72 (1H, dd, J=8.8, 1.5 Hz), 7.81 (1H, d, J=8.8 Hz),  
8.17 (1H, d, J=8.8 Hz), 8.20-8.31 (2H, m), 8.50 (1H, s).

Elementary analysis for C<sub>26</sub>H<sub>29</sub>ClIN<sub>3</sub>O<sub>3</sub>S·H<sub>2</sub>O

Calculated: C, 48.49; H, 4.85; N, 6.53.

Found: C, 48.66; H, 4.96; N, 6.39.

10 [Example B-54] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

A reaction was effected in the same manner as in Example B-7 by using 1-[(5-chloroindol-2-yl)sulfonyl]piperazine and lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxylate as starting materials, whereby the title compound was obtained as brown amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.49 (3H, s), 2.78-2.83 (2H, m), 2.85-  
20 2.94 (2H, m), 3.15-3.28 (4H, br), 3.67 (2H, s), 3.82-3.95 (2H, br),  
4.50-4.65 (2H, br), 6.96 (1H, d, J=2.0 Hz),  
7.32 (1H, dd, J=8.8, 2.0 Hz), 7.36 (1H, d, J=8.8 Hz), 7.67 (1H, s),  
8.71 (1H, br).

MS (FAB) m/z: 480 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 482 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

25 Elementary analysis for C<sub>20</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>3</sub>S<sub>2</sub>·HCl·0.5H<sub>2</sub>O

Calculated: C, 44.64; H, 4.76; Cl, 13.18; N, 13.02; S, 11.92.

Found: C, 44.69; H, 4.72; Cl, 13.36; N, 12.76; S, 11.76.

5 In a similar manner to Example B-54, the compounds shown in Examples B-55 to B-60 were synthesized.

[Example B-55] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
10 hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.50-2.63 (3H,m), 2.65-2.74 (2H,m), 2.92 (3H,s), 3.00-3.14 (2H,m), 3.22-3.42 (2H,m), 3.63-3.78 (2H,m), 4.23-4.29 (1H,m), 4.35-4.47 (1H,m), 4.64-4.80 (1H,m), 4.97-5.02 (1/2H,m), 5.45-5.51 (1H,m), 6.13-  
15 6.17 (1/2H,m), 7.02 (1H,br), 7.32 (1H,dd,J=8.8,2.0Hz), 7.47 (1H,d,J=8.3Hz), 7.77 (1H,br), 8.07-8.16 (1H,m), 12.41 (1H,s).

MS (FAB) m/z: 537 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 539 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>22</sub>H<sub>25</sub>ClN<sub>6</sub>O<sub>4</sub>S<sub>2</sub>·HCl·1.7H<sub>2</sub>O

20 Calculated: C, 43.74; H, 4.90; Cl, 11.74; N, 13.91; S, 10.62.

Found: C, 44.02; H, 5.07; Cl, 11.83; N, 13.59; S, 10.52.

[Example B-56] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)carbonyl]piperazine hydrochloride  
25

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.65 (3H, d, J=4.5Hz), 2.85-3.22 (7H, m),  
 3.22-3.38 (2H, m), 3.66 (1H, d, J=12.2Hz), 3.55-3.68 (2H, m),  
 4.17-4.40 (3H, m), 4.55-4.68 (1H, m), 6.99 (1H, d, J=2.0Hz), 7.27-  
 7.31 (2H, m), 7.48 (1H, d, J=8.8Hz), 7.77 (1H, d, J=2.0Hz),  
 8.09 (1H, br s), 10.60 (1H, br s), 12.41 (1H, s).

MS (FAB) m/z: 536 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 538 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>23</sub>H<sub>26</sub>ClN<sub>5</sub>O<sub>4</sub>S<sub>2</sub>·1.3HCl·0.6H<sub>2</sub>O·1.5EtOH

Calculated: C, 47.07; H, 5.70; Cl, 12.29; N, 10.56; S,  
 9.67.

Found: C, 46.68; H, 5.63; Cl, 12.16; N, 10.20; S,  
 10.06.

[Example B-57] 1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazine

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.91 (3H, s), 3.11 (2H, br), 3.25-  
 3.90 (4H, m), 3.76 (2H, br), 5.35-4.80 (2H, br), 4.41 (2H, br),  
 7.46 (1H, d, J=8.8Hz), 7.73 (1H, s), 7.84 (1H, d, J=8.8Hz),  
 7.96 (1H, s), 11.48 (1H, br).

MS (FAB) m/z: 481 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 483 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>20</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S<sub>2</sub>·1.1HCl·0.3H<sub>2</sub>O

Calculated: C, 45.63; H, 4.35; Cl, 14.14; N, 10.64; S,  
 12.18.

Found: C, 45.81; H, 4.29; Cl, 13.93; N, 10.44; S,  
 12.26.

[Example B-58] 1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]-4-

[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.91(3H,s), 3.00-3.55(7H,m), 3.60-3.85(3H,m), 4.42(3H,br), 4.67(1H,br), 7.46(1H,d,J=8.8Hz),  
 5 7.73(1H,s), 7.84(1H,d,J=8.8Hz), 7.96(1H,s), 11.48(1H,br).

MS (FAB) m/z: 481 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 483 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>20</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>4</sub>S<sub>2</sub>·HCl·0.17H<sub>2</sub>O

Calculated: C, 46.15; H, 4.33; Cl, 13.62; N, 10.76; S, 12.32.

10 Found: C, 46.45; H, 4.41; Cl, 13.61; N, 10.58; S, 12.02.

[Example B-59] 1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.91(3H,s), 2.98-3.90(10H,m), 4.24-4.77(4H,m), 7.60(1H,d,J=8.8Hz), 8.05(1H,s), 8.10-8.21(2H,m), 11.72(1H,br s).

MS (FAB) m/z: 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>20</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>3</sub>S<sub>3</sub>·HCl·0.9H<sub>2</sub>O

20 Calculated: C, 43.70; H, 4.36; Cl, 12.90; N, 10.19; S, 17.50.

Found: C, 43.82; H, 4.49; Cl, 13.27; N, 9.86; S, 17.32.

[Example B-60] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

25

yl)carbonyl]piperazine hydrochloride

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.91(3H,s), 3.02-3.25(5H,m), 3.32-3.90(6H,m), 4.33-4.55(2H,m), 4.64-4.75(1H,m), 7.55(1H,dd,J=8.8,2.0Hz), 8.06(1H,d,J=8.8Hz), 8.09(1H,s), 11.42(1H,br s).

MS (FAB)  $m/z$ : 497  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 499  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{20}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}_3 \cdot 1.1\text{HCl} \cdot 1.4\text{H}_2\text{O}$

Calculated: C, 42.71; H, 4.46; Cl, 13.24; N, 9.96; S, 17.11.

Found: C, 42.49; H, 4.51; Cl, 13.01; N, 9.76; S, 16.95.

[Example B-61] 2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine was treated and purified in the same manner as in Example B-33, whereby the title compound was obtained.

IR(KBr) $\text{cm}^{-1}$ : 3016, 1631, 1450, 1432, 1344, 1328, 1276, 1267, 1162, 1135, 998, 727, 578.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.10-3.23(4H,m), 3.85(2H,br s), 4.29(2H,br s), 4.48(3H,s), 7.70(1H,dd,J=8.8,2.0Hz), 7.83(1H,d,J=8.8,2.0Hz), 8.17(1H,d,J=8.8Hz), 8.23(1H,d,J=2.0Hz), 8.26(1H,d,J=8.8Hz), 8.52(1H,s), 8.71(1H,d,J=6.8Hz), 8.98(1H,d,J=6.8,2.0Hz),



9.92 (1H, d, J=2.0Hz) .

MS (FAB) m/z: 487 [M<sup>+</sup>, Cl<sup>35</sup>], 489 [M<sup>+</sup>, Cl<sup>37</sup>] .

[Example B-62] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
[(N-methyl)carbamoyl]-1-[(6-methyl-4,5,6,7-

5 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
hydrochloride

In N,N-dimethylformamide (100 ml), lithium 6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxylate (616  
mg), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[(N-  
10 methyl)carbamoyl]piperazine trifluoroacetate (1.12 g), 1-  
hydroxybenzotriazole monohydrate (36 mg) and 1-  
(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
(579 mg) were dissolved and the resulting solution was  
stirred overnight at room temperature. The reaction  
15 mixture was concentrated under reduced pressure.  
Dichloromethane was then added to the residue, followed by  
washing with water. The organic layer was dried over  
anhydrous sodium sulfate and distilled under reduced  
pressure to remove the solvent. The residue was purified  
20 by chromatography on a silica gel column [ $\Phi$  3.0 x (1.5 +  
8) cm, ethyl acetate : methanol = 100:4], whereby a  
colorless foam was obtained. The resulting foam was  
dissolved in 1N HCl (20 ml), followed by concentration  
under reduced pressure, whereby the title compound (845 mg)  
25 was obtained as a pale yellow foam.

IR(KBr)cm<sup>-1</sup>: 3380, 1668, 1623, 1542, 1415, 1342, 1330,

1159, 1135, 1078, 952, 941, 723, 578.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.42-2.80 (5H,m), 2.90 (3H,s), 2.95-3.80 (6H,m), 4.23-4.50 (5/2H,m), 4.60-4.77 (1H,m), 4.98 (1/2H,br s), 5.45-5.55 (1H,m), 6.15 (1/2H,br s), 7.71 (1H,d,J=8.8Hz), 7.78-7.82 (1H,m), 8.07-8.13 (1H,m), 8.15 (1H,d,J=8.8Hz), 8.23 (1H,s), 8.25 (1H,d,J=8.8Hz), 8.49 (1H,s), 11.70-12.00 (1H,m).

MS (FAB) m/z: 548 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 550 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

In a similar manner to Example B-62, the compounds of Examples B-63 to B-76 were obtained.

[Example B-63] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[[ (morpholin-4-yl)carbonyl]methyl]piperazine hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.35-2.83 (2H,m), 2.89 (3H,s), 2.95-3.88 (18H,m), 4.31-4.45 (3/2H,m), 4.67 (2H,d,J=15.1Hz), 5.03 (0.5H,br s), 5.37 (0.5H,d,J=13.7Hz), 5.79 (1/2H,br s), 7.70 (1H,dd,J=8.8,2.0Hz), 7.81 (1H,d,J=8.8Hz), 8.15 (1H,d,J=8.8Hz), 8.23 (1H,s), 8.27 (1H,d,J=8.8Hz), 8.50 (1H,s), 11.50-11.75 (1H,m).

MS (FAB) m/z: 618 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 620 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{28}H_{32}ClN_5O_5S_2 \cdot 1.5HCl \cdot 3H_2O$

Calculated: C, 46.27; H, 5.48; Cl, 12.19; N, 9.63; S, 8.82.

Found: C, 46.49; H, 5.20; Cl, 12.16; N, 9.67; S, 8.88.

[Example B-64] N-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-  
 5 1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazin-2-yl]carbonyl]glycine ethyl ester

Starting materials: lithium 6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, N-[[1-[(6-  
 chloronaphthalen-2-yl)sulfonyl]piperazin-3-  
 10 yl]carbonyl]glycine ethyl ester trifluoroacetate

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.17-1.24 (3H,m), 2.38 (3H,s), 2.39-  
 2.53 (1H,m), 2.58-2.84 (5H,m), 3.20-3.29 (1H,m), 3.54-  
 3.81 (4H,m), 3.90-4.00 (1H,m), 4.06-4.17 (1H,m),  
 4.32 (1H,d,J=11.7Hz), 4.47 (1/2H,d,J=13.7Hz), 5.14 (1/2H,s),  
 15 5.66 (1/2H,d,J=13.7Hz), 6.42 (1H,br s), 7.68 (1H,d,J=8.3Hz),  
 7.79 (1H,d,J=8.3Hz), 8.12 (1H,dd,J=8.8,3.4Hz), 8.19 (1H,s),  
 8.23 (1H,d,J=8.8Hz), 8.48 (1H,s), 8.52 (1/2H,t,J=5.4Hz),  
 8.61 (1/2H,t,J=5.4Hz).

MS (FD) m/z: 619 [ $M^+$ ,  $Cl^{35}$ ], 621 [ $M^+$ ,  $Cl^{37}$ ].

20 Elementary analysis for  $C_{27}H_{30}ClN_5O_6S_2 \cdot 0.2HCl \cdot 0.1H_2O$

Calculated: C, 51.54; H, 4.87; Cl, 6.76; N, 11.13; S,  
 10.19.

Found: C, 51.31; H, 4.92; Cl, 6.74; N, 10.92; S,  
 10.01.

25 In the present reaction, the below-described compound  
 whose ester bond had been hydrolyzed was obtained.

N-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]glycine

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.37(3H,s), 2.59-2.83(6H,m), 3.20-

5 3.32(1H,m), 3.52-3.77(4H,m), 3.82-3.95(1H,m), 4.28-

4.35(1H,m), 4.45(1/2H,d,J=13.7Hz), 5.13(1/2H,br s),

5.63(1/2H,d,J=13.7Hz), 6.36(1H,br s), 7.69(1H,d,J=8.3Hz),

7.80(1H,d,J=8.3Hz), 8.12(1H,dd,J=8.8,3.4Hz), 8.20(1H,s),

8.23(1H,d,J=8.8Hz), 8.41(1/2H,t,J=5.4Hz), 8.45-

10 8.50(3/2H,m).

MS (FD)  $m/z$ : 592 [(M+H) $^+$ , Cl $^{35}$ ], 594 [(M+H) $^+$ , Cl $^{37}$ ].

Elementary analysis for  $\text{C}_{27}\text{H}_{30}\text{ClN}_5\text{O}_6\text{S}_2 \cdot \text{H}_2\text{O}$

Calculated: C, 49.22; H, 4.63; Cl, 5.81; N, 11.48; S, 10.51.

15 Found: C, 49.11; H, 4.78; Cl, 6.02; N, 11.41; S, 10.25.

[Example B-65] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-(morpholin-4-yl)carbamoyl]piperazine hydrochloride

20

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[N-(morpholin-4-yl)carbamoyl]piperazine trifluoroacetate

25  $^1\text{H-NMR}$  (DMSO- $d_6$  at 100°C)  $\delta$ : 2.58-2.84(8H,m), 2.89(3H,s),

2.98-3.58 (3H,m), 3.40-3.80 (8H,m), 4.10-4.70 (4H,m),  
 7.65 (1H,dd,J=8.6,2.4Hz), 7.79 (1H,dd,J=8.6,1.2Hz),  
 8.09 (1H,d,J=8.6Hz), 8.14 (1H,s), 8.18 (1H,d,J=8.6Hz),  
 8.42 (1H,s), 8.58 (1H,br s).

5 MS (FAB) m/z: 619 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 621 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>24</sub>H<sub>26</sub>ClN<sub>4</sub>O<sub>5</sub>S<sub>2</sub>·1.7HCl·1.7H<sub>2</sub>O

Calculated: C, 45.56; H, 5.11; Cl, 13.45; N, 10.57; S,  
 8.93.

Found: C, 45.35; H, 5.34; Cl, 13.46; N, 12.01; S,

10 8.93.

[Example B-66] Ethyl N'-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)carbonyl]hydrazinoacetate

15 hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, ethyl N'-[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl)carbonyl]hydrazinoacetate hydrochloride

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.18-1.28 (3H,m), 2.36 (3H,s), 2.65-2.85 (5H,m), 3.23-3.28 (1H,m), 3.31 (2H,s), 3.44-3.75 (4H,m), 4.08-4.24 (3H,m), 4.38 (1/2H,d,J=13.7Hz), 5.01 (1/2H,s), 5.22-5.31 (1H,m), 5.52 (1/2H,d,J=13.7Hz), 6.10 (1/2H,br s), 7.69 (1H,d,J=8.8,2.0Hz), 7.72-7.80 (1H,m), 7.72-7.80 (3H,m),  
 25 8.47 (1H,s), 9.77-9.85 (1H,m).

MS (FAB) m/z: 635 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 637 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{27}H_{31}ClN_6O_6S_2 \cdot 1.6HCl \cdot H_2O$

Calculated: C, 45.58; H, 4.90; Cl, 12.95; N, 11.81; S, 9.01.

Found: C, 45.71; H, 5.09; Cl, 12.83; N, 11.46; S, 8.94.

[Example B-67] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine hydrochloride

Starting materials : lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[N-[(morpholin-4-yl)carbonyl]methyl]carbamoyl]piperazine hydrochloride

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.35-2.82 (2H,m), 2.90 (3H,s), 2.95-3.30 (2H,m), 3.32-3.86 (13H,m), 4.05-4.20 (1H,m), 4.23-4.50 (2.5H,m), 4.59-4.70 (1H,m), 5.15 (0.5H,s), 5.50 (0.5H,d,J=12.2Hz), 6.30 (0.5H,s), 7.70 (1H,dd,J=8.8,2.0Hz), 7.80 (1H,d,J=8.8Hz), 8.12-8.38 (4H,m), 8.48 (1H,s), 11.45-11.75 (1H,m).

MS (FAB) m/z: 661 [(M+H) $^+$ , Cl $^{35}$ ], 663 [(M+H) $^+$ , Cl $^{37}$ ].

Elementary analysis for  $C_{29}H_{33}ClN_6O_6S_2 \cdot HCl \cdot H_2O$

Calculated: C, 48.67; H, 5.07; Cl, 9.91; N, 11.74; S, 8.96.

Found: C, 48.70; H, 5.03; Cl, 10.23; N, 11.55; S, 9.32.

[Example B-68] 4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazin-2-yl]carbonyl]morpholine  
hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 4-[[1-[(6-  
5 chloronaphthalen-2-yl)sulfonyl]piperazin-3-  
yl]carbonyl]morpholine trifluoroacetate

IR(KBr)cm<sup>-1</sup>: 3396, 2919, 2854, 1652, 1623, 1457, 1112, 954,  
723, 578.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.62-2.79(1H,m), 2.85-3.92(19H,m),  
10 4.02-4.13(1/2H,m), 4.30-4.49(3/2H,m), 4.58-4.80(1H,m),  
5.24-5.46(1H,m), 6.28-6.45(1H,m), 7.71(1H,dd,J=8.8,2.0Hz),  
7.83(1H,d,J=8.8Hz), 8.12-8.28(3H,m), 8.53(1H,s), 11.30-  
11.80(1H,m).

MS (FAB) m/z: 604 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 606 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

15 [Example B-69] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

Starting materials: lithium 6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-  
20 chloronaphthalen-2-yl)sulfonyl]-3-  
[ethoxycarbonyl]piperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.25-1.35(3H,m), 2.43-2.94(9H,m),  
3.31(1/2H,dt,J=12.7,3.4Hz), 3.60-3.76(2.5H,m),  
3.83(1/2H,d,J=11.7Hz), 3.89(1/2H,d,J=11.7Hz), 4.19-  
25 4.30(2H,m), 4.42-4.50(1H,m), 4.55(1/2H,14.2Hz),

5.76 (1/2H, 14.2Hz), 7.57 (1H, dd, J=8.3, 1.5Hz),  
7.77 (1H, dd, J=8.3, 1.5Hz), 7.89-7.94 (3H, m), 8.34 (1H, s).

MS (FAB) m/z: 563 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 565 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-70] Methyl [4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetate

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-

[methoxycarbonylmethyl]piperazine

IR(KBr)cm<sup>-1</sup>: 2944, 2846, 2788, 1735, 1619, 1455, 1164.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.40-2.92 (10H, m),

3.04 (1H, dd, J=16.1, 8.8Hz), 3.16-3.27 (1/2H, m), 3.42-

3.55 (1/2H, m), 3.60-3.72 (5H, m), 3.83-3.97 (2H, m),

4.60 (1/2H, d, J=13.2Hz), 5.21 (1/2H, br s),

5.70 (1/2H, d, J=13.2Hz), 6.15 (1/2H, br s),

7.57 (1H, dd, J=8.8, 2.0Hz), 7.75 (1H, dd, J=8.8, 2.0Hz), 7.87-

7.95 (3H, m), 8.30 (1H, s).

MS (FAB) m/z: 563 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 565 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-71] 2-[[N-(tert-butoxy)amino]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

Starting materials: lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-chloronaphthalen-2-yl)sulfonyl]-3-[(N-tert-



butoxy)carbonyl]piperazine trifluoroacetate

IR(KBr)cm<sup>-1</sup>: 2979, 1675, 1465, 1199, 1184, 1166, 1135, 721.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.15-1.25(9H,m), 2.36(3H,s), 2.37-

2.49(1H,m), 2.67-2.84(5H,m), 3.25-3.35(1H,m), 3.59-

5 3.78(3H,m), 4.13-4.25(1H,m), 4.38(1H,d,J=13.2Hz),

5.01(1/2H,br s), 5.52(1/2H,d,J=13.2Hz), 5.14(1/2H,s),

6.21(1/2H,br s), 7.69(1H,dd,J=8.8,2.0Hz), 7.76-7.74(1H,m),

8.14(1H,d,J=8.8Hz), 8.21(1H,s), 8.24(1H,d,J=8.8Hz), 8.47-

8.53(1H,m), 10.75-10.78(1H,m).

10 MS (FAB) m/z: 606 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 608 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-72] [4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-  
[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-yl]acetamide hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-

15 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-  
chloronaphthalen-2-yl)sulfonyl]-3-

[carbamoylmethyl]piperazine hydrochloride

IR(KBr)cm<sup>-1</sup>: 1671, 1616, 1465, 1457, 1419, 1332, 1162,  
1133, 1124, 1078, 956, 701, 578.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.30-2.80(4H,m), 2.90(3H,s), 2.93-

3.25(2H,m), 3.30-3.55(1H,m), 3.62-3.88(3H,m), 4.05-

4.43(2.5H,m), 4.60-4.71(1H,m), 5.05(0.5H,br s),

5.34(0.5H,d,J=13.2Hz), 5.69-5.84(0.5H,m), 6.82(0.5H,br s),

6.93(0.5H,br s), 7.37-7.50(1H,m), 7.70(1H,d,J=8.8Hz),

25 7.80(1H,d,J=8.8Hz), 8.10-8.29(3H,m), 8.49(1H,s).

MS (FAB) m/z: 576 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 578 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-73] 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-  
[(N-isopropyl)carbamoyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
5 hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-  
chloronaphthalen-2-yl)sulfonyl]-3-[(N-  
isopropyl)carbamoyl]piperazine hydrochloride

10 IR(KBr)cm<sup>-1</sup>: 2967, 2933, 1666, 1625, 1542, 1463, 1344,  
1332, 1159, 1135, 954, 725, 578.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.00-1.10(6H,m), 2.50-2.80(2H,m),  
2.91(3H,s), 2.93-3.50(4H,m), 3.60-3.79(2H,m), 3.82-  
3.95(1H,m), 4.18-4.30(1H,m), 4.32-4.50(1.5H,m), 4.60-  
15 4.77(1H,m), 4.97(0.5H,s), 5.03(0.5H,d,J=13.2Hz),  
5.90(0.5H,s), 7.70(1H,d,J=8.8Hz), 7.79(1H,d,J=8.8Hz), 7.92-  
8.00(1H,m), 8.22(1H,d,J=8.8Hz), 8.18-8.28(2H,m),  
8.48(1H,s).

MS (FAB) m/z: 576 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 578 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example B-74] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
[[piperidin-1-yl)carbonyl]methyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-  
25 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-  
chloronaphthalen-2-yl)sulfonyl]-3-[[piperidin-1-

yl)carbonyl)methyl]piperazine hydrochloride

IR(KBr)cm<sup>-1</sup>: 2931, 2854, 1623, 1455, 1334, 1159, 1135, 1124, 1078, 954, 700, 578.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.20-1.70(8H,m), 2.35-2.82(2H,m),  
 2.90(3H,s), 2.95-3.88(11H,m), 4.31-4.45(1.5H,m), 4.62-  
 4.76(1H,m), 5.03(0.5H,br s), 5.34(0.5H,d,J=13.2Hz),  
 5.70(0.5H,br s), 7.70(1H,d,J=8.8Hz), 7.81(1H,d,J=8.8Hz),  
 8.15(1H,d,J=8.8Hz), 8.22(1H,s), 8.27(1H,d,J=8.8Hz),  
 8.50(1H,s).

MS (FAB) m/z: 616 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 618 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-75] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
 [[N-(2-methoxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 hydrochloride

Starting materials: lithium 6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate, 1-[(6-  
 chloronaphthalen-2-yl)sulfonyl]-3-[[N-(2-  
 methoxybenzyl)]carbamoyl]piperazine hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.42-3.54(9H,m), 3.62-3.85(5H,m), 4.12-  
 4.50(3.5H,m), 4.60-4.77(1H,m), 5.09(1/2H,br s), 5.43-  
 5.52(1/2H,m), 6.11-6.19(1/2H,m), 6.85-7.00(2H,m), 7.16-  
 7.29(2H,m), 7.72(1H,d,J=10.7Hz), 7.80-7.86(1H,m),  
 8.16(1H,d,J=8.8Hz), 8.22-8.28(2H,m), 8.50(1H,s), 8.65-  
 8.72(1H,m).

MS (FAB) m/z: 654 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 656 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-76] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
 [[N-(2-methoxyethyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 hydrochloride

5           Starting materials: lithium 6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate,  
 4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-  
 methoxyethyl)]carbamoyl]piperazine  
 IR(KBr)  $\text{cm}^{-1}$ : 2931, 1544, 1463, 1423, 1344, 1332, 1157,  
 10   1133, 1078, 954, 943, 723, 578.  
 $^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.42-2.82 (2H,m), 2.92 (3H,s), 2.95-  
 3.79 (13H,m), 4.21-4.80 (3.5H,m), 5.02 (1/2H,br s),  
 5.47 (1/2H,d,J=12.2Hz), 6.07 (1/2H,br s),  
 7.70 (1H,dd,J=8.8,2.0Hz), 7.79 (1H,d,J=8.8Hz),  
 15   8.13 (1H,d,J=8.8Hz), 8.17-8.32 (3H,m), 8.48 (1H,s), 11.09-  
 11.40 (1H,m).  
 MS (FAB)  $m/z$ : 592 [(M+H) $^+$ , Cl $^{35}$ ], 594 [(M+H) $^+$ , Cl $^{37}$ ].

[Example B-77] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 20   yl)carbonyl]piperazine-2-carboxylic acid

In tetrahydrofuran (10 ml), 4-[(6-chloronaphthalen-2-  
 yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 (2.08 g) was dissolved, followed by the addition of ethanol  
 25   (20 ml) and a 1N aqueous solution (3.70 ml) of sodium  
 hydroxide. The resulting mixture was stirred at room

temperature for 1 hour. After concentration of the reaction mixture under reduced pressure, the residue was added with water (20 ml). The precipitate thus formed was collected by filtration, whereby the title compound (1.39 g) was obtained as a pale yellow foam.

IR(KBr)cm<sup>-1</sup>: 1731, 1625, 1461, 1346, 1332, 1315, 1159, 1135, 1078, 954, 943, 723, 580.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.32-3.86(11H,m), 4.27(1H,d,J=11.7Hz), 4.35-4.48(3/2H,m), 4.59-4.78(1H,m), 5.21(1/2H,m), 5.38-5.52(1/2H,m), 6.34-6.47(1/2H,m), 7.71(1H,dd,J=8.8,2.0Hz), 7.83(1H,d,J=8.8Hz), 8.16(1H,d,J=8.8Hz), 8.23(1H,s), 8.27(1H,d,J=8.8Hz), 8.53(1H,s), 11.60-11.90(1H,m).

Elementary analysis for C<sub>23</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>5</sub>S<sub>2</sub>·1.3HCl·1.5H<sub>2</sub>O

Calculated: C, 45.33; H, 4.51; Cl, 13.38; N, 9.19; S, 10.52.

Found: C, 45.69; H, 4.55; Cl, 13.29; N, 9.21; S, 10.21.

[Example B-78] N'-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetic acid

In the same manner as in the Example B-77, the title compound was obtained using ethyl N'-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetate hydrochloride as a starting material.

MS (FAB) m/z: 607 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 609 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> at 100°C) δ: 2.41 (3H, s), 2.65-3.30 (6H, m), 3.37-3.77 (8H, m), 4.16 (1H, d, J=12.7 Hz), 7.64 (1H, dd, J=8.7, 2.4 Hz), 7.78 (1H, dd, J=8.7, 1.6 Hz), 8.07 (1H, d, J=8.7 Hz), 8.11 (1H, d, J=1.6 Hz), 8.16 (1H, d, J=8.7 Hz), 8.42 (1H, s).

Elementary analysis for C<sub>25</sub>H<sub>27</sub>ClN<sub>5</sub>O<sub>6</sub>S<sub>2</sub>·2H<sub>2</sub>O

Calculated: C, 46.69; H, 4.86; N, 13.07; S, 9.97.

Found: C, 46.87; H, 4.86; N, 12.82; S, 9.62.

[Example B-79] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-(tetrahydropyran-2-yloxy)]carbamoyl]piperazine

In N,N-dimethylformamide (20 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid (141 mg), 2-tetrahydropyranyloxyamine (180 mg), 1-hydroxybenzotriazole monohydrate (11 mg), 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (145 mg) and potassium carbonate (129 mg) were dissolved,

followed by stirring overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Dichloromethane was added to the residue, followed by washing with water. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column ( $\Phi$  0.7 x 25.0 cm, dichloromethane : methanol = 100:3), whereby the title compound (308 mg) was obtained as a colorless foam.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.50-1.89(6H,m), 2.45-2.55(3H,m), 2.72-3.00(6H,m), 3.57-3.97(5H,m), 4.28(0.5H,d,J=12.2Hz), 4.35(0.5H,d,J=12.2Hz), 4.52-4.61(0.5H,m), 4.92(0.5H,s), 5.02(0.5H,br s), 5.06-5.10(0.5H,m), 5.55-5.65(0.5H,m), 5.88(0.5H,br s), 6.21(0.5H,br s), 7.51-7.58(1H,m), 7.77-7.93(4H,m), 8.35(1H,s), 9.61(0.5H,br s), 10.10(1H,br s). MS (FAB) m/z: 634 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 636 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-80] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carbohydroxamic acid

In methanol (10 ml), 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[N-(tetrahydropyran-2-yloxy)]carbamoyl]piperazine (297 mg) was dissolved, followed by the addition of 1N hydrochloric acid (10 ml). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced

pressure. The residue was purified by "HP-20" ( $\Phi$  1.7 x 20.0 cm, acetonitrile : water = 1:5), whereby the title compound (65 mg) was obtained as a pale yellow foam.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.32-2.73 (2H, m), 2.91 (3H, s), 2.97-  
 5 3.30 (3H, m), 3.35-3.50 (1H, m), 3.63-3.76 (2H, m), 4.22-  
 4.48 (2.5H, m), 4.61-4.75 (1H, m), 4.99 (0.5H, s),  
 5.47 (0.5H, d,  $J=12.2\text{Hz}$ ), 6.24 (0.5H, s), 7.70 (1H, d,  $J=8.8\text{Hz}$ ),  
 7.75-7.85 (1H, m), 8.15 (1H, d,  $J=8.8\text{Hz}$ ), 8.23 (1H, s),  
 8.25 (1H, d,  $J=8.8\text{Hz}$ ), 8.48 (1H, s), 10.26 (1H, br s), 10.97 (1H, br  
 10 s).

MS (FAB)  $m/z$ : 550  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 552  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example B-81] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
 [[N-(2-hydroxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 In dichloromethane (10 ml), 4-[(6-chloronaphthalen-2-  
 yl)sulfonyl]-2-[[N-(2-methoxybenzyl)]carbamoyl]-1-[(6-  
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazine hydrochloride (195 mg) was  
 dissolved, followed by the dropwise addition of a boron  
 20 tribromide - dichloromethane solution (1.0M, 2.08 ml) at -  
 78°C. The reaction mixture was heated to room temperature  
 and stirred overnight. To the reaction mixture, methanol  
 (2 ml), sodium carbonate (200 mg) and water (3 ml) were  
 added to extract the organic layer, followed by drying over  
 25 anhydrous sodium sulfate. The solvent was then distilled  
 off under reduced pressure. The solid thus precipitated



was collected by filtration while being washed with 1N hydrochloric acid, whereby the title compound (50 mg, 24%) was obtained as a pale yellow solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.36-2.87(9H,m), 3.11-3.28(1H,m), 3.59-  
 5 3.80(3H,m), 4.12-4.45(3.5H,m), 4.48-4.57(1/2H,m),  
 5.08(1/2H,br s), 6.19(1/2H,br s), 6.63-6.81(2H,m), 6.98-  
 7.15(2H,m), 7.70(1H,dd,J=8.3,1.5Hz), 7.78-7.84(1H,m),  
 8.13(1H,d,J=8.8Hz), 8.20-8.28(2H,m), 8.49(1H,s), 8.50-  
 8.62(1H,m), 9.45(1/2H,s), 9.50(1/2H,s).

10 MS (FAB) m/z: 640 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 642 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-82] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine hydrochloride

To a solution of 6-methyl-4,5,6,7-tetrahydrofuro[2,3-  
 15 c]pyridine (58.1 mg) in tetrahydrofuran (3.2 ml), n-butyl lithium (a 1.59N hexane solution, 320 μl) was added at -78°C, followed by stirring for 1 hour and then at 0°C for 30 minutes. The reaction mixture was cooled to -78°C and a carbon dioxide gas was introduced therein for 1 hour.  
 20 After the reaction mixture was heated to room temperature over 30 minutes, it was concentrated. To a solution of the resulting residue in N,N-dimethylformamide (6.0 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (177 mg, 510 μmol) was dissolved, followed by the addition  
 25 of 1-(dimethylaminopropyl)-3-ethylcarbodiimide (98.0 mg,

511  $\mu$ mol) and 1-hydroxybenzotriazole (69.0 mg, 511  $\mu$ mol) at room temperature and then, diisopropylethylamine (185  $\mu$ l, 1.06 mmol) at 0°C. After stirring overnight at room temperature, the reaction mixture was added with methylene chloride (20 ml) and a saturated aqueous solution (50 ml) of sodium bicarbonate, whereby the organic layer was separated. The resulting organic layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, washed with water (50 ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified twice by preparative thin-layer chromatography on a silica gel (methylene chloride : acetone : methanol = 10:5:1). The white solid thus obtained was dissolved in a 1N ethanol hydrochloride solution and the resulting solution was concentrated. After the addition of water, the mixture was concentrated again, whereby the title compound (74.7 mg) was obtained as a white solid.

IR(KBr)cm<sup>-1</sup>: 3396, 2918, 2850, 2538, 1620, 1456, 1432, 1344, 1329, 1282, 1161, 955, 941, 729.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 2.68(1H, br d, J=15.1Hz), 2.78-2.92(1H, br), 2.85(3H, s), 3.04(4H, br s), 3.26(1H, br s), 3.52(1H, br s), 3.72(4H, br s), 4.20(1H, br d, J=15.1Hz), 4.43(1H, br d, J=15.1Hz), 6.92(1H, s), 7.71(1H, dd, J=2.0, 8.8Hz), 7.80(1H, d, J=8.8Hz),

8.15 (1H, d, J=8.8Hz), 8.23 (1H, s), 8.25 (1H, d, J=8.8Hz),  
8.48 (1H, s), 11.64 (1H, br s).

MS (FAB) m/z: 474 [(M+H)<sup>+</sup>].

Elementary analysis for C<sub>23</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>4</sub>S·1.1HCl·1.7H<sub>2</sub>O

5 Calculated: C, 50.72; H, 5.27; N, 7.71; Cl, 13.67; S, 5.89.

Found: C, 50.58; H, 5.39; N, 7.69; Cl, 13.94; S, 5.85.

[Example B-83] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride

10 To 6-(t-butoxycarbonyl)-2-[[4-(chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine (1.28 g, 2.24 mmol), a saturated ethanol hydrochloride solution (50 ml) was added at room temperature. The resulting mixture was stirred for 20  
15 minutes, followed by concentration, whereby the title compound (1.26 g) was obtained as a white solid.

IR(KBr)cm<sup>-1</sup>: 3396, 2924, 2615, 2544, 1957, 1655, 1610, 1473, 1454, 1425, 1448, 1336, 1286, 1157, 941, 731, 580.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.02 (2H, br t, J=5.3Hz),

20 3.05 (2H, t, J=6.4Hz), 3.42-3.49 (2H, brm), 3.52 (2H, br t, J=5.3Hz), 3.75 (2H, br t, J=5.3Hz), 4.33 (2H, br t, J=5.3Hz), 7.56 (1H, br d, J=8.3Hz), 7.89 (1H, d, J=8.3Hz), 7.89 (1H, dd, J=1.5, 8.8Hz), 7.98 (1H, dd, J=2.0, 8.8Hz), 8.34 (1H, d, J=8.8Hz), 8.43 (1H, s), 8.44 (1H, d, J=8.8Hz),  
25 8.67 (1H, br s), 9.87 (2H, br s).

MS (FAB) m/z: 471 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for  $C_{23}H_{23}ClN_4O_3S \cdot 1.9HCl \cdot 0.9H_2O$

Calculated: C, 49.64; H, 4.84; Cl, 10.07; N, 18.48; S, 5.76.

Found: C, 49.64; H, 4.96; Cl, 10.01; N, 18.73; S, 5.93.

[Example B-84] 2-[[4-(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride

To a solution of 2-[[4-(chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine (174 mg) in methylene chloride (3.5 ml), triethylamine (95.6  $\mu$ l), acetic acid (58.9  $\mu$ l), formaldehyde (a 37% aqueous solution, 42.0  $\mu$ l) and sodium triacetoxymethylborohydride (110 mg) were added at room temperature, followed by stirring for 15 minutes. To the reaction mixture, a saturated aqueous solution (10 ml) of sodium bicarbonate and methylene chloride (10 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on a silica gel (methylene chloride : methanol = 15:1). The white solid thus obtained was dissolved in a 1N aqueous hydrochloride in ethanol,

followed by concentration, whereby the title compound (170 mg) was obtained as a white solid.

IR(KBr)  $\text{cm}^{-1}$ : 3359, 2918, 2544, 1655, 1641, 1475, 1431, 1342, 1331, 1284, 1155, 953, 941, 727, 579.

5  $^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.04 (3H, d,  $J=3.9\text{Hz}$ ), 3.17 (2H, br s), 3.26 (2H, br s), 3.38-3.65 (2H, m), 3.68 (2H, br s), 3.39 (2H, br s), 4.40-4.70 (2H, m), 4.57 (2H, br s), 7.57 (1H, d,  $J=7.8\text{Hz}$ ), 7.84-7.92 (2H, m), 7.98 (1H, d,  $J=8.8\text{Hz}$ ), 8.33 (1H, d,  $J=8.3\text{Hz}$ ), 8.42 (1H, s), 8.43 (1H, d,  $J=8.8\text{Hz}$ ), 8.67 (1H, s), 11.86 (1H, br s).  
10 MS (FAB)  $m/z$ : 485 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ].

[Example B-85] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

A saturated solution of hydrochloride in ethanol (25 ml) was added to 1,5-bis(*t*-butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (300 mg) at room temperature, followed by stirring for 1 hour. The reaction mixture was concentrated and water was added to the concentrate. The resulting mixture was concentrated under reduced pressure. To the residue, a saturated solution of hydrochloride in methanol (25 ml) was added at room temperature, followed by stirring for 1 hour. After concentration of the reaction mixture, water was added and the resulting mixture was concentrated under reduced pressure, whereby the title compound (200 mg) was obtained

as a white solid.

IR(KBr)cm<sup>-1</sup>: 3290, 2918, 2762, 2559, 1614, 1483, 1454, 1381, 1340, 1323, 1244, 1155, 1147, 1136, 978, 955, 727, 575.

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.77(2H,br t,J=5.9Hz),  
3.03(4H,t,J=5.3Hz), 3.30(2H,br t,J=5.9Hz), 3.73(4H,br  
t,J=5.3Hz), 3.99(2H,br s), 6.32(1H,d,J=2.0Hz),  
7.73(1H,dd,J=2.0,8.8Hz), 7.83(1H,dd,J=2.0,8.8Hz),  
8.17(1H,d,J=8.8Hz), 8.25(1H,d,J=2.0Hz), 8.28(1H,d,J=8.8Hz),  
10 8.50(1H,br s), 9.07(2H,br), 11.38(1H,br).

MS (FAB) m/z: 459 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for C<sub>22</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>3</sub>S·1.1HCl·0.3H<sub>2</sub>O

Calculated: C, 52.38; H, 4.94; N, 11.11; Cl, 14.76; S, 6.36.

15 Found: C, 52.48; H, 4.92; N, 11.07; Cl, 14.48; S, 6.65.

[Example B-86] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

20 In methylene chloride (4.5 ml), 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (200 mg) was suspended, followed by the addition of triethylamine (125 μl), acetic acid (77.0 μl),

25 formaldehyde (a 37% aqueous solution, 56.1 μl) and sodium

triacetoxyborohydride (139 mg) at room temperature. The resulting mixture was stirred for 15 minutes. To the reaction mixture, a saturated aqueous solution (20 ml) of sodium bicarbonate and methylene chloride (10 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (25 g of silica gel, methylene chloride : methanol = 10:1 → 7:1). The resulting solid was dissolved in a 1N aqueous hydrochloride in ethanol. After concentration of the resulting solution, water was added to the concentrate and the mixture was concentrated again, whereby the title compound (133 mg) was obtained as a white solid.

IR(KBr)cm<sup>-1</sup>: 3213, 2918, 2650, 2530, 1604, 1585, 1508, 1491, 1456, 1342, 1331, 1157, 727, 579.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.72-2.86(1H,m), 2.83(3H,d,J=4.9Hz), 2.87-2.99(1H,m), 3.03(4H,br t,J=4.4Hz), 3.19-3.31(1H,m), 3.46-3.64(1H,m), 3.74(4H,br t,J=4.4Hz), 3.97(1H,dd,J=7.8,14.2Hz), 4.20(1H,br d,J=14.2Hz), 6.32(1H,d,J=2.4Hz), 7.72(1H,dd,J=2.4,8.8Hz), 7.82(1H,dd,J=2.0,8.8Hz), 8.16(1H,d,J=8.8Hz), 8.25(1H,d,J=2.0Hz), 8.27(1H,d,J=8.8Hz), 8.51(1H,br s), 10.84(1H,br s), 11.42(1H,br s).

MS (FAB)  $m/z$ : 473  $[(M+H)^+, Cl^{35}]$ .

Elementary analysis for  $C_{23}H_{25}ClN_4O_3S \cdot 1.3HCl \cdot 0.7H_2O$

Calculated: C, 51.83; H, 5.24; N, 10.51; Cl, 15.30; S, 6.02.

5 Found: C, 51.83; H, 5.37; N, 10.30; Cl, 15.35; S, 6.09.

[Example B-87] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

10 In methylene chloride (3.0 ml), 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (149 mg) was suspended, followed by the addition of methanol (0.6 ml), triethylamine (82.5  $\mu$ l), acetic acid  
15 (51.0  $\mu$ l, 891  $\mu$ mol), acetaldehyde (19.5  $\mu$ l) and sodium triacetoxyborohydride (74.0 mg) at room temperature. The resulting mixture was stirred for 15 minutes. To the reaction mixture, a saturated aqueous solution (30 ml) of sodium bicarbonate and methylene chloride (15 ml) were  
20 added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on  
25 a silica gel column (30 g of silica gel, methylene



chloride : methanol = 10:1). The resulting white solid was dissolved in a 1N aqueous hydrochloride in ethanol (10 ml). After concentration of the resulting solution, water (30 ml) was added to the concentrate and the mixture was concentrated again, whereby the title compound (81.7 mg) was obtained as a white solid.

IR(KBr)  $\text{cm}^{-1}$ : 3386, 3226, 2918, 2586, 1603, 1585, 1491, 1454, 1427, 1344, 1331, 1163, 1136, 1078, 933, 727, 579.

$^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$ : 1.26(3H, t,  $J=7.3\text{Hz}$ ), 2.72-2.82(1H, m), 2.86-3.00(1H, m), 3.02(4H, br s), 3.12-3.64(6H, m), 3.73(4H, br s), 3.96(1H, dd,  $J=7.8, 14.1\text{Hz}$ ), 4.22(1H, br d,  $J=14.1\text{Hz}$ ), 6.31(1H, d,  $J=2.4\text{Hz}$ ), 7.71(1H, br d,  $J=8.8\text{Hz}$ ), 7.81(1H, br d,  $J=8.8\text{Hz}$ ), 8.16(1H, d,  $J=8.8\text{Hz}$ ), 8.23(1H, br s), 8.26(1H, d,  $J=8.8\text{Hz}$ ), 8.50(1H, br s), 10.39(1H, br s), 11.40(1H, br s).

MS (FAB)  $m/z$ : 486  $[(M+H)^+, \text{Cl}^{35}]$ .

Elementary analysis for  $\text{C}_{24}\text{H}_{27}\text{ClN}_4\text{O}_3\text{S} \cdot 1.2\text{HCl} \cdot 2.0\text{H}_2\text{O}$

Calculated: C, 50.86; H, 5.73; N, 9.88; Cl, 13.76; S, 5.66.

Found: C, 51.11; H, 5.71; N, 9.58; Cl, 13.60; S, 5.66.

[Example B-88] 5-(*t*-Butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine

In methylene chloride (15 ml), 2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine hydrochloride (780 mg) was suspended, followed by the addition of a

saturated aqueous solution (15 ml) of sodium bicarbonate and di-*t*-butyl dicarbonate (506 ml) at room temperature. The resulting mixture was stirred for 1 hour. To the reaction mixture, water (30 ml) and methylene chloride (30 ml) were added to separate the water layer. The resulting water layer was extracted with methylene chloride (2 x 20 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (75 g of silica gel, methylene chloride : acetone = 8:1 → 2:1). The resulting white solid was dissolved in a 1N aqueous hydrochloride in ethanol. After concentration of the resulting solution, water was added to the concentrate and the mixture was concentrated again, whereby the title compound (641 mg) was obtained as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.46(9H,s), 2.61(2H,br s), 3.12(4H,br t, J=4.9Hz), 3.66(2H,br s), 3.90(4H,br t, J=4.9Hz), 4.36(2H,br s), 6.19(1H,d, J=2.0Hz), 7.57(1H,dd, J=1.7, 9.0Hz), 7.76(1H,br d, J=8.8Hz), 7.86-7.97(3H,m), 8.29(1H,br s), 9.24(1H,br s).

[Example B-89] 5-(*t*-Butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-*c*]pyridine

To a solution of 5-(*t*-butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-

4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (33.0 mg) in N,N-dimethylformamide (15 ml), sodium hydride (60% in oil, 3.5 mg) was added at 0°C. After stirring for 10 minutes, methyl iodide (4.5  $\mu$ l) was added and the resulting mixture was stirred at 0°C for 1 hour. To the reaction mixture, a saturated aqueous solution (10 ml) of ammonium chloride, methylene chloride (20 ml) and water (30 ml) were added to separate the organic layer. The resulting water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on a silica gel (methylene chloride : acetone = 9:1), whereby the title compound (32.3 mg) was obtained as a colorless, transparent viscous substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.46(9H,s), 2.58(2H,br s), 3.12(4H,br t, J=4.5Hz), 3.50(3H,s), 3.68(2H,br s), 3.84(4H,br t, J=4.5Hz), 4.32(2H,br s), 6.02(1H,s), 7.58(1H,dd, J=2.0, 8.8Hz), 7.77(1H,dd, J=1.7, 8.5Hz), 7.88-7.97(3H,m), 8.32(1H,br s).

[Example B-90] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

To 5-(t-butoxycarbonyl)-2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine (280 mg), a saturated

solution hydrochloride in ethanol (25 ml) was added at room temperature, followed by stirring for 1 hour. The reaction mixture was then concentrated. Water (10 ml) was added to the concentrate, followed by concentration under reduced pressure, whereby the title compound (210 mg) was obtained as a white solid.

IR(KBr)  $\text{cm}^{-1}$ : 3381, 2918, 2748, 1622, 1583, 1495, 1454, 1342, 1331, 1248, 1163, 1136, 953, 935, 879, 726, 579, 476.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.81(2H, br t,  $J=5.6\text{Hz}$ ), 3.05(4H, br s), 3.35(2H, br t,  $J=5.6\text{Hz}$ ), 3.42(3H, s), 3.69(4H, br s), 3.97(2H, br s), 6.18(1H, s), 7.73(1H, dd,  $J=2.0, 8.8\text{Hz}$ ), 7.83(1H, dd,  $J=2.0, 8.8\text{Hz}$ ), 8.18(1H, d,  $J=8.8\text{Hz}$ ), 8.27(1H, br s), 8.28(1H, d,  $J=8.8\text{Hz}$ ), 8.50(1H, br s), 9.34(1H, br d,  $J=27.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 473 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ].

Elementary analysis for  $\text{C}_{23}\text{H}_{25}\text{ClN}_4\text{O}_3\text{S}\cdot 1.4\text{HCl}\cdot 1.2\text{H}_2\text{O}$

Calculated: C, 50.63; H, 5.32; N, 10.27; Cl, 15.59; S, 5.88.

Found: C, 50.71; H, 5.53; N, 10.14; Cl, 15.53; S, 5.90.

[Example B-91] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,5-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride

In methylene chloride (10 ml), 2-[[4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1-methyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine hydrochloride (170 mg) was suspended, followed by the

addition of methanol (10 ml), triethylamine (100  $\mu$ l),  
acetic acid (62.0  $\mu$ l), formaldehyde (a 37% aqueous  
solution, 46.5  $\mu$ l) and sodium triacetoxyborohydride (115  
mg) at room temperature. The resulting mixture was stirred  
5 for 30 minutes. To the reaction mixture, a saturated  
aqueous solution (50 ml) of sodium bicarbonate and  
methylene chloride (30 ml) were added to separate the water  
layer. The water layer thus obtained was extracted with  
methylene chloride (2 x 10 ml). The organic layers were  
10 combined, dried over anhydrous sodium sulfate and  
concentrated under reduced pressure. The residue was  
purified by chromatography on a silica gel column (30 g of  
silica gel, methylene chloride : methanol = 10:1  $\rightarrow$  7:1).  
The resulting white solid was dissolved in a 1N aqueous  
15 hydrochloride in ethanol. After the concentration of the  
resulting solution, water was added to the concentrate and  
the resulting mixture was concentrated again, whereby the  
title compound (162 mg) was obtained as a white solid.  
IR(KBr)cm<sup>-1</sup>: 3396, 2924, 2663, 2586, 1622, 1581, 1456,  
20 1342, 1329, 1248, 1163, 1136, 955, 937, 727, 579.  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 2.77-3.00(5H,m), 3.06(4H,br s), 3.23-  
3.37(1H,m), 3.43(3H,s), 3.55-3.65(1H,m), 3.69(4H,br s),  
3.90-4.03(1H,m), 3.93(3H,s), 4.19(1H,br d,J=11.7Hz),  
6.18(1H,s), 7.74(1H,dd,J=2.0,8.8Hz),  
25 7.83(1H,dd,J=2.0,8.8Hz), 8.18(1H,d,J=8.8Hz), 8.27(1H,br s),

8.28 (1H, d, J=8.8 Hz), 8.51 (1H, br s), 11.00 (1H, br s).

MS (FAB) m/z: 487 [(M+H)<sup>+</sup>, Cl<sup>35</sup>].

Elementary analysis for C<sub>24</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub>S·1.4HCl·1.4H<sub>2</sub>O

Calculated: C, 51.18; H, 5.58; N, 9.95; Cl, 15.11; S, 5.69.

5 Found: C, 51.09; H, 5.83; N, 9.78; Cl, 15.37; S, 5.79.

[Example B-92] 2-(N-Methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

In N,N-dimethylformamide (5 ml) was dissolved 3-(N-methylcarbamoyl)-1-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine (218 mg), followed by the addition of lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (188 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (240 mg) and 15 1-hydroxybenzotriazole (68 mg). The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with methylene chloride, washed with water (twice) and then with a saturated aqueous solution of sodium bicarbonate. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced 20 pressure. The residue was purified by chromatography on a silica gel column (methanol : methylene chloride = 3:97 → 5:95 → 7:93), whereby the title compound (90 mg) was obtained.

25 MS (FAB) m/z: 616 (M+H)<sup>+</sup>.

[Example B-93] 4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-2-[N-methylcarbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In a mixed solvent of tetrahydrofuran (0.5 ml) and methanol (0.5 ml) was dissolved 2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl]piperazine (90 mg), followed by the addition of a 1N aqueous solution (0.3 ml) of sodium hydroxide. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was made weakly acidic with a saturated aqueous solution of ammonium chloride and then made weakly alkaline with a saturated aqueous solution of sodium bicarbonate. The solution was extracted (four times) with methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (methanol : methylene chloride = 1:9). Similar reaction and post treatment were repeated three times and the purified products were combined, followed by purification through Sephadex LH-20 (elution with methanol). The amorphous substance thus obtained was dissolved in methylene chloride. Hexane was added dropwise to the resulting solution, whereby the title compound (82 mg) was obtained as a light gray solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.49(3H,s), 2.80-2.90(10H,m), 3.15-3.18(1H,m), 3.22(1H,s), 3.53-3.62(1H,m), 3.67(1H,s), 4.49(1H,d,J=12.2Hz), 4.65, 5.74(total 1H,each d,J=13.7Hz), 5.26, 6.18(total 1H,each s), 6.45, 6.49(total 1H,each s),  
 5 7.54(1H,d,J=8.3Hz), 7.80(1H,s), 7.82(1H,d,J=8.3Hz),  
 7.97(1H,s).

MS (FAB)  $m/z$ : 544 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-94] 1-[(6-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl]piperazine  
 10 (morpholin-4-yl)carbonyl]methyl]piperazine

In methylene chloride (5 ml) was dissolved 1-(tert-butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl]piperazine (930 mg),  
 15 followed by the addition of trifluoroacetic acid (2 ml). The resulting mixture was stirred at room temperature for 30 minutes. A saturated aqueous solution of sodium bicarbonate was added and the resulting mixture was extracted with methylene chloride. The organic layer was  
 20 dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in N,N-dimethylformamide (10 ml), followed by the addition of lithium 6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (695 mg),  
 25 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (506 mg) and 1-hydroxybenzotriazole (119 mg). The



resulting mixture was stirred overnight at room temperature. A saturated aqueous solution of sodium bicarbonate was added and the resulting mixtures was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 1:1), whereby the title compound (585 mg) was obtained as an orange foam.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48 (9H, s), 2.58-3.96 (19H, m), 4.60-6.02 (4H, m), 6.98 (1H, s), 7.27 (1H, d, J=9.0Hz), 7.38 (1H, d, J=9.0Hz), 7.64 (H, s), 10.39 (1H, s).

[Example B-95] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine

In methylene chloride (5 ml) was dissolved 1-[(6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-

[[ (morpholin-4-yl)carbonyl]methyl]piperazine (585 mg),

followed by the addition of trifluoroacetic acid (2 ml).

The resulting mixture was stirred at room temperature for 30 minutes. A saturated aqueous solution of sodium

bicarbonate was added and the resulting mixture was

extracted with methylene chloride (to which N,N-

dimethylformamide was added in a small amount). The

organic layer was dried over anhydrous sodium sulfate and

distilled under reduced pressure to remove the solvent. To the residue was added a 1N aqueous hydrochloride in ethanol (1 ml) and the solvent was distilled off under reduced pressure, whereby the hydrochloride (585 mg, containing two molecules of N,N-dimethylformamide). A 100 mg portion of the resulting hydrochloride was added to methylene chloride (3 ml), followed by the addition of triethylamine (0.5 ml) and methanesulfonyl chloride (20 mg). The resulting mixture was stirred at room temperature for 2 hours. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture. The resulting mixture was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (methylene chloride : methanol = 9:1). The solid thus obtained was dissolved in methylene chloride, followed by the addition of ether for crystallization, whereby the title compound (34.2 mg) was obtained as a white solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.33-3.57(20H,m), 3.72-3.79(2H,m), 4.38, 5.39(total 1H,each d,J=12.2,13.7Hz), 4.55(2H,s), 5.06, 5.82(total 1H,each br s), 7.02(1H,s), 7.30(1H,d,J=8.8Hz), 7.47(1H,d,J=8.8Hz), 7.76(1H,s), 12.41(1H,s).

MS (FAB) m/z: 671 (M+H)<sup>+</sup>.

[Example B-96] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-

methylcarbamoyl)-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

In N,N-dimethylformamide (50 ml) were dissolved 6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid (530 mg), 4-[(5-chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine hydrochloride (527 mg) and 1-hydroxybenzotriazole monohydrate (200 mg) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (324 mg), followed by the addition of triethylamine (0.18 ml). The resulting mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Methylene chloride was added to the residue and the resulting mixture was washed with water and saturated aqueous NaCl solution, each once. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 100:1), whereby pale yellow foam (577 mg) was obtained. The resulting foam was dissolved in methylene chloride (3 ml), followed by the addition of trifluoroacetic acid (6 ml). The resulting mixture was concentrated under reduced pressure. The precipitate so formed was collected by filtration while being washed with diethyl ether, whereby the title compound (596 mg) was obtained as colorless foam.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.53-2.62 (3H,m), 2.63-2.74 (1H,m), 2.90-3.06 (2H,m), 3.12-3.22 (0.5H,m), 3.39-3.59 (1.5H,s), 3.68-3.77 (1H,m), 4.28 (1H,d,J=11.7Hz), 4.28-4.50 (1.5H,m), 4.97 (0.5H,br s), 5.44 (0.5H,d,J=13.2Hz), 6.13 (0.5H,br s), 7.72 (1H,dd,J=8.8,2.0Hz), 7.80 (1H,d,J=8.8Hz), 8.07-8.18 (2H,m), 8.22-8.27 (2H,m), 8.50 (1H,s), 9.16-9.40 (1H,m). MS (FAB) m/z: 534 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 536 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-97] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-95, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.61-2.87 (1H,m), 2.88 (6H,br s), 2.89-3.24 (3H,m), 3.45-3.90 (4H,m), 4.43-4.60 (3H,m), 4.74, 5.21 (total 1H,each br s), 5.60-6.09 (total 1H,m), 6.30, 6.42 (total 1H,br s), 7.58 (1H,d,J=7.6Hz), 7.80 (1H,d,J=9.0Hz), 7.89-7.91 (3H,m), 8.35 (1H,s). MS (FAB) m/z: 612 (M+H)<sup>+</sup>.

[Example B-98] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-dimethylaminosulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[morpholin-4-yl)carbonyl]methyl]piperazine

In the same manner as in Example B-95, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.60-3.79 (25H,m), 4.38, 5.37 (total

1H, each d, J=13.5, 14.5Hz), 4.53 (2H, s), 5.04, 5.75 (total  
 1H, each br), 7.02 (1H, s), 7.30 (1H, dd, J=8.8, 2.0Hz),  
 7.47 (1H, d, J=8.8Hz), 7.76 (1H, s), 12.41 (1H, s).  
 MS (FAB) m/z: 700 (M+H)<sup>+</sup>.

5 [Example B-99] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-  
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine  
 hydrochloride

To an ethanol solution (50 ml) of 1-(tert-  
 10 butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-  
 [[ (morpholin-4-yl)carbonyl]methyl]piperazine (710 mg) was  
 added a saturated ethanol hydrochloride solution (20 ml) at  
 room temperature. The resulting mixture was stirred for 3  
 hours. After concentration of the reaction mixture under  
 15 reduced pressure, diethyl ether and ethanol were added to  
 precipitate crystals. The resulting crystals were  
 collected by filtration, washed with ethanol and then dried  
 under reduced pressure. The crystals were dissolved in  
 N,N-dimethylformamide to form an N,N-dimethylformamide  
 20 solution (50 ml), followed by the addition of 1-  
 hydroxybenzotriazole (68.8 mg), 1-(3-dimethylaminopropyl-3-  
 ethylcarbodiimide hydrochloride (115.4 mg), lithium 6-  
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-  
 carboxylate (189.0 mg) and N-methylmorpholine (140.5 mg) at  
 25 room temperature. The resulting mixture was stirred at  
 room temperature for 19 hours. The reaction solvent was

distilled off under reduced pressure. Distilled water and ethyl acetate were added to the residue and the water layer was extracted three times. The organic layers were combined, washed four times with distilled water, dried  
 5 over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methanol : ethyl acetate = 1:50). Diethyl ether and methylene chloride were added to the purified product to precipitate crystals. The  
 10 resulting crystals were collected by filtration, followed by washing with diethyl ether. A 1N aqueous hydrochloric acid in ethanol (0.5 ml) and a small amount of distilled water were added. The solvent was then distilled off under reduced pressure. The residue was dried under heat at 60°C  
 15 under reduced pressure, whereby the title compound (187 mg) was obtained as a yellow amorphous solid.

MS (FAB<sup>+</sup>) m/z: 607 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 609 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.66-2.89(1H,m), 2.99(3H,s), 3.03-  
 3.29(2H,m), 3.34-3.46(1H,m), 3.52-3.92(8H,m), 4.42-  
 20 4.53(1.5H,m), 4.73-4.81(1H,m), 5.10-5.17(0.5H,m), 5.39-  
 5.47(1H,m), 5.82-5.92(0.5H,m), 7.12(1H,br),  
 7.41(1H,dd,J=2.0,8.8Hz), 7.58(1H,d,J=8.8Hz), 7.87(1H,br),  
 12.57(1H,s).

[Example B-100] 2-(Carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-98, the title compound was obtained.

MS (FAB<sup>+</sup>) m/z: 537 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 539 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.00-1.08(1H,m), 2.65-2.68(1H,m), 2.88-  
 5 2.94(2H,m), 3.00-3.12(1H,m), 3.27-3.46(3H,m), 3.62-  
 3.73(1H,m), 4.32-4.39(1H,m), 5.04-5.37(1H,m), 6.83-  
 6.86(1H,m), 7.01(1H,s), 7.27-7.33(1H,m),  
 7.46(1H,d,J=8.5Hz), 7.76(1H,s), 12.42(1H,s).

[Example B-101] 1-[(5-Chloroisoindolin-2-yl)sulfonyl]-4-  
 10 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonylpiperazine hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

MS (FAB<sup>+</sup>) m/z: 482 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 484 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.93(3H,s), 3.08-3.19(1H,m), 3.28-  
 3.40(8H,m), 3.40-3.53(1H,br), 3.68-3.77(2H,br), 4.28-  
 4.46(2H,m), 4.63-4.65(4H,m), 7.33(1H,d,J=8.3Hz),  
 7.37(1H,dd,J=2.0,8.3Hz), 7.41(1H,s).

[Example B-102] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-  
 20 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonylpiperazine

A saturated solution of hydrochloride in ethanol (8.0 ml) was added to 1-(tert-butoxycarbonyl)-4-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 25 yl)carbonylpiperazine (300 mg). After stirring for 1

hour, the reaction mixture was concentrated under reduced pressure. To the residue were added N,N-dimethylformamide (8.0 ml) and 1-phenylsulfonyl-5-trimethylsilylethynylindol-2-sulfonyl chloride (450 mg) at room temperature, followed  
5 by the addition of diisopropylethylamine (860  $\mu$ l) at 0°C. After stirring at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone : methanol = 30:10:1  
10  $\rightarrow$  10:10:1), whereby 4-[(6-methyl-4,5,6,7-tetrahydrothizolo[5,4-c]pyridin-2-yl)carbonyl]-1-[(1-phenylsulfonyl-5-trimethylsilylethynylindol-2-yl)carbonyl]piperazine (123 mg) was obtained as a colorless viscous substance. The resulting substance was dissolved  
15 in tetrahydrofuran (3.0 ml), followed by the addition of methanol (3.0 ml) and potassium hydroxide (22.5 mg) at room temperature. After stirring for 2 hours, a saturated aqueous solution (10 ml) of ammonium chloride was added. A saturated aqueous solution (15 ml) of sodium bicarbonate  
20 and methylene chloride (10 ml) were added and the mixture was separated into layers. The water layer was extracted with methylene chloride (10 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue  
25 was purified by preparative thin-layer chromatography (methylene chloride : acetone : methanol = 40:10:1) using



silica gel, whereby the title compound (39.4 mg) was obtained as a colorless solid. The resulting compound was dissolved in methylene chloride, methanol and water. The resulting solution was concentrated under reduced pressure, followed by drying, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.49(3H,s), 2.81(2H,t,J=5.5Hz), 2.90(2H,t,J=5.5Hz), 3.04(1H,s), 3.22(4H,br s), 3.68(2H,s), 3.88(2H,br s), 4.57(2H,br s), 7.00(1H,s), 7.37(1H,d,J=8.6Hz), 7.47(1H,dd,J=8.6,1.5Hz), 7.86(1H,s), 8.88(1H,br s).

MS (FAB)  $m/z$ : 470 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-103] 2-(N-Methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(1-phenylsulfonyl-5-trimethylsilylethynylindol-2-yl)sulfonyl]piperazine

A saturated solution of hydrochloride in methanol (20 ml) was added to 4-(tert-butoxycarbonyl)-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine (410 mg) at room temperature. After stirring for 1 hour, the reaction mixture was concentrated under reduced pressure. To the residue were added methylene chloride (15 ml) and 1-phenylsulfonyl-5-trimethylsilylethynylindol-2-sulfonyl chloride (450 mg) at room temperature, followed by the addition of diisopropylethylamine (590  $\mu\text{l}$ ) at room

temperature. After stirring for 12 hours,  
 diisopropylethylamine (590  $\mu$ l) was added again at room  
 temperature. The resulting mixture was stirred at room  
 temperature for 4 hours. A saturated aqueous solution (50  
 5 ml) of sodium bicarbonate and methylene chloride (50 ml)  
 were added to the reaction mixture and the mixture was  
 separated into layers. The water layer was extracted with  
 methylene chloride (2 x 20 ml). The organic layers were  
 combined, dried over anhydrous sodium sulfate and distilled  
 10 under reduced pressure to remove the solvent. The residue  
 was purified by chromatography on a silica gel column  
 (methylene chloride : methanol = 20:1), whereby the title  
 compound (389 mg) was obtained as a colorless transparent  
 glassy substance.

15  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.25 (9H, s), 2.50 (3H, d,  $J=8.3\text{Hz}$ ), 2.65-  
 3.02 (8H, m), 3.05-3.30 (2H, m), 3.70 (2H, br s),  
 4.13 (1H, d,  $J=13.4\text{Hz}$ ), 4.40 (1H, d,  $J=13.4\text{Hz}$ ),  
 4.67 (1/2H, d,  $J=13.4\text{Hz}$ ), 5.24 (1/2H, br s),  
 5.66 (1/2H, d,  $J=14.0\text{Hz}$ ), 6.08 (1/2H, br s), 6.39 (1H, br s),  
 20 7.41 (2H, t,  $J=7.7\text{Hz}$ ), 7.47-7.63 (3H, m), 7.71 (1H, s),  
 8.02 (2H, d,  $J=7.8\text{Hz}$ ), 8.18 (1H, d,  $J=8.8\text{Hz}$ ).  
 MS (FAB)  $m/z$ : 739 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-104] 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(*N*-  
 methylcarbamoyl)-1-[(6-methyl-4,5,6,7-  
 25 tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)carbonyl]piperazine

In tetrahydrofuran (5.0 ml) was dissolved 2-[(*N*-

methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(1-phenylsulfonyl-5-trimethylsilylethynylindol-2-yl)carbonyl]piperazine (350 mg), followed by the addition of methanol (5.0 ml) and potassium hydroxide (102 mg) at room temperature. After stirring for 4 hours, a saturated aqueous solution (50 ml) of sodium bicarbonate and methylene chloride (50 ml) were added to the reaction mixture to separate the mixture into layers. The water layer was extracted with methylene chloride (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified twice by chromatography on a silica gel column (methylene chloride : methanol = 20:1), whereby the title compound (126 mg) was obtained as a colorless solid. The resulting solid was dissolved in methylene chloride, methanol and water, followed by concentration under reduced pressure and drying, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.51 (3H, s), 2.75-3.30 (11H, m), 3.58-3.85 (3H, m), 4.50-4.70 (2H, m), 5.25 (1/2H, brs), 5.64 (1/2H, d,  $J=11.5\text{Hz}$ ), 6.10 (1/2H, br s), 6.53 (1/2H, br s), 7.10 (1H, s), 7.43 (2H, s), 7.85 (1H, s), 10.78 (1H, d,  $J=9.5\text{Hz}$ ).  
MS (FAB)  $m/z$ : 527 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-105] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-

yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.92(3H,s), 3.04-3.28(6H,m), 3.35-  
 5 3.90(4H,m), 4.12-4.70(4H,m), 7.69(1H,dd,J=8.8,2.0Hz),  
 7.82(1H,dd,J=8.8,2.0Hz), 8.14(1H,d,J=8.8Hz), 8.21(1H,s),  
 8.25(1H,dd,dd,J=8.8,2.0Hz), 8.50(1H,s), 11.27(1H,br s).  
 MS (FAB) m/z: 491 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 493 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-106] 4-[(5-Chloronaphthalen-2-yl)sulfonyl]-2-  
 10 (N-methylcarbamoyl)-1-[(5-methyl-4,5,6,7-  
 tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine  
 hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.43-2.81(5H,m), 2.89-2.95(4H,m), 3.22-  
 3.80(6H,m), 4.16-4.65(2.5H,m), 5.01(0.5H,s), 5.36-  
 5.45(0.5H,m), 6.06(0.5H,br s), 7.00(1H,s),  
 7.29(1H,d,J=8.8Hz), 7.48(1H,d,J=8.8Hz), 7.75(1H,s), 11.25-  
 11.40(1H,m), 12.43(1H,s).

20 MS (FAB) m/z: 537 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 539 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-107] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-  
 methylcarbamoyl)-1-[(5-isopropyl-4,5,6,7-  
 tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine  
 hydrochloride

25 In the same manner as in Example B-62, the title

compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.31-1.40 (6H,m), 2.38-2.75 (5H,m), 3.10-3.80 (8H,m), 4.22-4.50 (2.5H,m), 4.97 (1/2H,br s), 5.35-5.49 (1/2H,m), 6.13 (1/4H,br s), 6.19 (1/4H,br s),  
 5 7.70 (1H,d,J=8.8Hz), 7.79 (1H,d,J=8.8Hz), 8.09-8.28 (4H,m),  
 8.49 (1H,s), 10.80-11.34 (1H,m).

MS (FAB) m/z: 576 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 578 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-108] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.20 (4H,br s), 3.84 (2H,br s),  
 4.35 (2H,br s), 7.28 (1H,dd,J=8.8,2.5Hz),  
 7.47 (1H,dd,J=8.8,2.0Hz), 7.74 (1H,d,J=2.0Hz),  
 15 8.05 (1H,d,J=5.4Hz), 8.67 (1H,d,J=5.4Hz), 9.44 (1H,s),  
 12.41 (1H,s).

MS (FAB) m/z: 462 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 464 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-109] 2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-  
 20 c]pyridinium iodide

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.14-3.28 (4H,m), 3.86 (2H,br s),  
 4.29 (2H,br s), 4.49 (3H,s), 7.04 (1H,s),  
 25 7.30 (1H,dd,J=8.8,2.0Hz), 7.48 (1H,d,J=8.8Hz), 7.76 (1H,s),

8.72 (1H, d, J=6.8Hz), 9.00 (1H, d, J=6.8Hz), 9.94 (1H, s),  
12.44 (1H, br s).

MS (FAB) m/z: 476, 478.

[Example B-110] 1-[(6-tert-Butoxycarbonyl-7-methyl-  
5 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-  
[(5-chloroindol-2-yl)sulfonyl]-2-(N-  
methylcarbamoyl)piperazine hydrochloride

In the same manner as in Example B-62, the title  
compound was obtained.

10 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.38 (3H, d, J=6.6Hz), 1.42 (9H, s), 2.55-  
2.80 (5H, m), 3.31 (3H, s), 3.46-3.56 (1/2H, m), 3.61-3.72 (1H, m),  
3.81-3.90 (1H, m), 4.18-4.29 (2H, m), 4.43-4.48 (1/2H, m), 4.91-  
5.05 (1H, m), 5.26-5.45 (1H, m), 6.15-6.25 (2H, m), 6.98-  
7.03 (1H, m), 7.26-7.33 (1H, m), 7.41-7.50 (1H, m), 7.73-  
15 7.80 (1H, m), 8.02-8.17 (1H, m), 12.40 (1H, s).

MS (FAB) m/z: 637 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 639 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-111] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-  
methylcarbamoyl)-1-[(7-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
20 trifluoroacetate

In the same manner as in Example B-35, the title  
compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.55 (3H, d, J=6.4Hz), 2.28-2.76 (5H, m),  
2.88-3.10 (2H, m), 3.25-3.65 (1H, m), 4.20-4.30 (1H, m), 4.40-  
25 4.50 (1/2H, m), 4.83 (1H, br s), 4.92-5.02 (1/2H, m), 5.40-

5.50 (1/2H,m), 6.13 (1/2H,s), 7.00 (1H,s), 7.30 (1H,d,J=8.8Hz),  
7.46 (1H,d,J=8.8Hz), 7.76 (1H,s), 8.06-8.14 (1H,m), 8.93-  
9.62 (2H,m), 12.40 (1H,s).

MS (FAB) m/z: 537 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 539 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example B-112] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-  
dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-2-(N-methylcarbamoyl)piperazine hydrochloride

In the same manner as in Example B-32, the title  
compound was obtained.

10 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.40-1.70 (3H,m), 2.40-2.80 (4H,m),  
2.92 (3H,br s), 3.00-3.25 (2H,m), 3.40-3.80 (1H,m), 4.19-  
4.30 (1H,m), 4.39-4.50 (1/2H,m), 4.66-4.82 (1/2H,br s),  
5.00 (1/2H,br s), 5.40-5.55 (1/2H,m), 5.73 (1/2H,br s),  
6.17 (1/2H,br s), 7.00 (1H,s), 7.30 (1H,d,J=8.8Hz),  
15 7.46 (1H,d,J=8.8Hz), 7.76 (1H,s), 8.05-8.20 (1H,m),  
12.41 (1H,s).

MS (EI) m/z: 550 (M<sup>+</sup>, Cl<sup>35</sup>), 552 (M<sup>+</sup>, Cl<sup>37</sup>).

[Example B-113] 2-[N-[(5-Acetoxy-4-oxo-4H-pyran-2-  
yl)methyl]carbamoyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-  
20 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

In the same manner as in Example B-62, the title  
compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> at 100°C) δ: 2.22 (3H,s), 2.38 (3H,s), 2.65-  
25 2.89 (8H,m), 3.64 (2H,s), 3.70 (1H,d,J=11.0Hz),

4.28 (1H, d, J=12.4Hz), 6.30 (1H, s), 6.98 (1H, s),  
 7.26 (1H, dd, J=9.2, 1.8Hz), 7.46 (1H, d, J=9.2Hz),  
 7.70 (1H, d, J=1.8Hz), 8.28 (1H, s), 8.51 (1H, s), 12.00 (1H, br s).  
 MS (FAB) m/z: 689 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 691 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5

[Example B-114] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[N-[(5-hydroxy-4-oxo-4H-pyran-2-yl)methyl]carbamoyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-23, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> at 100°C) δ: 2.71-2.84 (1H, m), 2.90 (3H, s),  
 3.00 (1H, dd, J=12.2, 4.3Hz), 3.06-3.28 (4H, m), 3.54 (2H, br s),  
 3.74 (1H, d, J=12.0Hz), 4.09-4.28 (4H, m), 4.52 (2H, br s),  
 7.00 (1H, d, J=1.2Hz), 7.29 (1H, dd, J=9.2, 1.8Hz),  
 7.50 (1H, d, J=9.2Hz), 7.73 (1H, d, J=1.8Hz), 7.91 (1H, s),  
 8.60 (1H, s), 12.14 (1H, br s).

15

MS (FAB) m/z: 647 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 649 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-115] N-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-  
 20 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetyl]methanesulfonamide hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

25

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.61-3.10 (8H, m), 3.15 (3H, s), 3.34-



3.81 (4H,m), 3.90-4.48 (2.5H,m), 4.60-4.72 (1H,m),  
 5.10 (0.5H,br s), 5.29-5.39 (0.5H,m), 5.80-6.00 (0.5H,m),  
 7.02 (1H,s), 7.30 (1H,d,J=8.8Hz), 7.48 (1H,d,J=8.8Hz),  
 7.75 (1H,s), 11.45-11.70 (1H,m), 11.85-12.00 (1H,m),  
 5 12.46 (1H,br s).

MS (FAB) m/z: 615 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 617 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-116] N-[[1-[(6-tert-Butoxycarbonyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-  
 chloroindol-2-yl)sulfonyl]piperazin-2-  
 10 yl]acetyl]methanesulfonamide

In the same manner as in Example B-62, the title  
 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.40 (9H,s), 2.62-2.93 (6H,m), 3.09-  
 3.20 (3H,m), 3.40-3.50 (0.5H,m), 3.60-3.78 (4.5H,m), 4.35-  
 15 4.43 (0.5H,m), 4.61 (2H,s), 5.07-5.14 (0.5H,m), 5.30-  
 5.40 (0.5H,m), 5.90-6.00 (0.5H,m), 7.03 (1H,s),  
 7.29 (1H,dd,J=8.8,2.0Hz), 7.45 (1H,d,J=8.8Hz), 7.74 (1H,s),  
 11.84 (1H,br s), 12.39 (1H,br s).

MS (FAB) m/z: 701 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 703 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-117] N-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-  
 [(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazin-1-yl]acetyl]methanesulfonamide  
 trifluoroacetate

In the same manner as in Example B-35, the title  
 25 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.64-3.04 (6H,m), 3.15 (3H,d,J=7.1Hz),

3.41-3.53 (2H, m), 3.60-3.80 (4H, m), 4.35-4.43 (0.5H, m),  
 4.44 (2H, s), 5.06-5.12 (0.5H, m), 5.25-5.35 (0.5H, m),  
 5.86 (0.5H, br s), 7.02 (1H, s), 7.29 (1H, dd, J=8.8, 2.0 Hz),  
 7.46 (1H, d, J=8.8 Hz), 7.75 (1H, s), 9.25 (2H, br s), 11.86 (1H, br  
 5 s), 12.42 (1H, br s).

MS (FAB) m/z: 601 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 603 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-118] N-[[1-[[6-(1-Acetoxyethoxy)carbonyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-  
 [(5-chloroindol-2-yl)sulfonyl]piperazin-2-  
 10 yl]acetyl]methanesulfonamide

In ethanol (2 ml) was dissolved N-[[4-[(5-chloroindol-  
 2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-  
 c]pyridin-2-yl)carbonyl]piperazin-2-  
 yl]acetyl]methanesulfonamide trifluoroacetate (97 mg),  
 15 followed by the addition of triethylamine (0.63 ml) and 1-  
 acetoxyethyl p-nitrophenyl carbonate (110 mg). The  
 resulting mixture was stirred at room temperature for 4  
 hours. The reaction mixture was concentrated under reduced  
 pressure. Methylene chloride was added to the residue.

20 The resulting mixture was washed with water, dried over  
 anhydrous sodium sulfate and distilled to remove the  
 solvent. The residue was purified by chromatography on a  
 silica gel column (methylene chloride : methanol = 50:1),  
 whereby the title compound (50 mg) was obtained as a  
 25 colorless foam.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.42 (3H, br s), 2.01 (3H, br s), 2.60-

2.90 (6H,m), 3.07-3.16 (3H,m), 3.64-3.80 (4H,m), 4.09-  
 4.12 (0.5H,m), 4.35-4.41 (0.5H,m), 4.63-4.77 (2.5H,m), 5.05-  
 5.11 (0.5H,m), 5.32-5.39 (0.5H,m), 5.89-5.96 (0.5H,m), 6.62-  
 6.70 (1H,m), 7.02 (1H,s), 7.29 (1H,d,J=8.8Hz),  
 5 7.46 (1H,d,J=8.8Hz), 7.75 (1H,s), 11.88 (1H,br s), 12.44 (1H,br  
 s).

MS (FAB) m/z: 731 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 733 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-119] 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
 2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-  
 10 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 hydrochloride

In the same manner as in Example B-62, the title  
 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.62 (3H,s), 2.66-4.49 (13.5H,m), 4.60-  
 15 4.76 (1H,m), 5.05 (1/2H,br s), 5.50-5.62 (1/2H,m), 6.15-  
 6.27 (1/2H,m), 7.57 (1H,d,J=8.8Hz), 8.07 (1H,d,J=8.8Hz),  
 8.08 (1H,s), 8.17 (1/2H,br s), 8.23 (1/2H,br s), 8.37 (1H,s).  
 MS (FAB) m/z: 554 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 556 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-120] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-  
 20 [(thiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title  
 compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.27 (4H,br s), 3.90-4.03 (2H,m), 4.61-  
 4.73 (2H,m), 7.58 (1H,dd,J=8.8,2.0Hz),  
 25 7.79 (1H,dd,J=8.8,2.0Hz), 7.85-8.01 (4H,m), 8.34 (1H,s),

8.59 (1H, d, J=5.4 Hz), 9.35 (1H, d, J=1.0 Hz).

MS (FAB) m/z: 473 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 475 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-121] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazolo[4,5-c]pyridine  
5 N-oxide

In the same manner as in Example B-34, the title compound was obtained.

H-NMR (DMSO-d<sub>6</sub>) δ: 3.15 (4H, br s), 3.80 (2H, br s), 4.32 (2H, br s), 7.70 (1H, dd, J=8.8, 2.0 Hz), 7.83 (1H, dd, J=8.8, 2.0 Hz),  
10 8.15 (1H, d, J=8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.22 (1H, s),  
8.25 (1H, d, J=8.8 Hz), 8.30 (1H, d, J=2.0 Hz), 8.32 (1H, d, J=1.5 Hz),  
8.51 (1H, s), 9.03 (1H, d, J=1.5 Hz).

MS (FAB) m/z: 489 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 491 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-122] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-5-methylthiazolo[4,5-c]pyridinium iodide  
15

In the same manner as in Example B-33, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.10-3.25 (4H, m), 3.85 (2H, br s),  
20 4.29 (2H, br s), 4.47 (3H, s), 7.71 (1H, dd, J=8.8, 2.0 Hz),  
7.84 (1H, d, J=8.8 Hz), 8.17 (1H, d, J=8.8 Hz), 8.23 (1H, s),  
8.26 (1H, d, J=8.8 Hz), 8.53 (1H, s), 8.86 (1H, d, J=6.8 Hz),  
8.90 (1H, d, J=6.8 Hz), 10.03 (1H, s).

MS (FAB) m/z: 487, 489.

[Example B-123] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-

(N-methylcarbamoyl)-1-[(thiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

5  $^1\text{H}$ -NMR (DMSO- $d_6$  at 100°C)  $\delta$ : 2.61 (3H, d,  $J=4.9\text{Hz}$ ), 2.75-2.88 (1H, m), 2.98 (1H, dd,  $J=12.7, 4.9\text{Hz}$ ), 3.20-3.80 (1H, m), 4.29 (1H, d,  $J=2.7\text{Hz}$ ), 4.90-5.48 (1H, m), 7.61 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.79 (1H, br s), 7.81 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.04-8.10 (2H, m), 10 8.12 (1H, d,  $J=5.4\text{Hz}$ ), 8.15 (1H, d,  $J=8.8\text{Hz}$ ), 8.44 (1H, d,  $J=1.0\text{Hz}$ ), 8.56 (1H, d,  $J=5.4\text{Hz}$ ), 9.28 (1H, br s).

MS (FAB)  $m/z$ : 530  $[(M+H)^+, \text{Cl}^{35}]$ , 532  $[(M+H)^+, \text{Cl}^{37}]$ .

[Example B-124] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazin-1-yl]carbonyl]-5-methylthiazolo[4,5-c]pyridinium Iodide  
15

In the same manner as in Example B-33, the title compound was obtained.

$^1\text{H}$ -NMR (DMSO- $d_6$  at 100°C)  $\delta$ : 2.62 (3H, d,  $J=4.4\text{Hz}$ ), 2.77-2.87 (1H, m), 2.94-3.03 (1H, m), 3.10-3.90 (2H, m), 20 4.31 (1H, d,  $J=12.7\text{Hz}$ ), 4.50 (3H, s), 4.85-5.85 (2H, m), 7.64 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.80 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.82-7.90 (1H, m), 8.10 (1H, d,  $J=8.8\text{Hz}$ ), 8.12 (1H, d,  $J=2.0\text{Hz}$ ), 8.17 (1H, d,  $J=8.8\text{Hz}$ ), 8.45 (1H, s), 8.86 (2H, d,  $J=1.5\text{Hz}$ ), 9.93 (1H, br s).

25 MS (FAB)  $m/z$ : 544 ( $M^+$ ,  $\text{Cl}^{35}$ ), 546 ( $M^+$ ,  $\text{Cl}^{37}$ ).

[Example B-125] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

5           The title compound was obtained in the same manner as in Referential Example 404 in which reduction by sodium borohydride had been employed.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.41-2.80 (5H,m), 3.12-3.78 (7H,m), 4.15-4.60 (2.5H,m), 4.97 (0.5H,br s), 5.35-5.48 (0.5H,m),  
10 6.03 (0.5H,br s), 7.70 (1H,dd,J=8.8,2.0Hz),  
7.79 (1H,d,J=8.8Hz), 8.06-8.20 (2H,m), 8.22 (1H,s),  
8.24 (1H,d,J=8.8Hz), 8.48 (1H,s), 11.20-11.63 (1H,m).  
MS (FAB) m/z: 548 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 550 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-126] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-  
15 [(6-ethyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine hydrochloride

In the same manner as in Referential Example 404, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.28-1.40 (3H,m), 2.40-2.79 (5H,m), 3.10-  
20 3.83 (10H,m), 4.15-4.60 (2.5H,m), 4.97 (0.5H,br s), 5.35-5.45 (0.5H,m), 6.05-6.12 (0.5H,m), 7.70 (1H,dd,J=8.8,2.0Hz),  
7.79 (1H,d,J=8.8Hz), 8.05-8.17 (2H,m), 8.22 (1H,s),  
8.24 (1H,d,J=8.8Hz), 8.49 (1H,s), 11.01-11.20 (1H,m).  
MS (FAB) m/z: 562 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 564 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

25 [Example B-127] tert-Butyl [2-[[4-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-6-yl)acetate

In N,N-dimethylformamide (50 ml) was dissolved 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-

5 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
hydrochloride (240 mg), followed by the addition of  
triethylamine (0.28 ml) and then tert-butyl bromoacetate  
(0.14 ml). The resulting mixture was stirred overnight at  
room temperature. After concentration of the reaction  
10 mixture under reduced pressure, ethyl acetate was added to  
the residue. The resulting mixture was washed with water,  
dried over anhydrous sodium sulfate and distilled under  
reduced pressure to remove the solvent. The residue was  
purified by chromatography on a silica gel column ( $\Phi$  3.0 x  
15 12.0 cm, hexane : ethyl acetate = 3:2), whereby the title  
compound (207 mg) was obtained as a colorless foam.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47 (9H, s), 2.86-2.92 (2H, m),  
3.00 (2H, t,  $J=5.4\text{Hz}$ ), 3.18 (4H, br s), 3.35 (2H, s), 3.87 (2H, br  
s), 3.90 (2H, s), 4.55 (2H, br s), 7.57 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
20 7.76 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.87-7.93 (3H, m), 8.31 (1H, s).

MS (FAB)  $m/z$ : 591  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 593  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example B-128] Ethyl [2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-6-yl)acetate

25 In the same manner as in Example B-127, the title  
compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.28 (3H, t, J=7.3 Hz), 2.85-2.95 (2H, m),  
 2.97-3.07 (2H, m), 3.18 (4H, br s), 3.46 (2H, s), 3.87 (2H, br s),  
 3.92 (2H, s), 4.20 (2H, q, J=7.3 Hz), 4.55 (2H, br s),  
 7.57 (1H, d, J=8.8 Hz), 7.76 (1H, d, J=8.8 Hz), 7.82-7.95 (3H, m),  
 8.31 (1H, s).

MS (FAB) m/z: 477 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 479 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-129] [2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl)acetic acid  
 trifluoroacetate

In methylene chloride (1 ml) was dissolved tert-butyl [2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl)acetate (200 mg), followed by the addition of  
 trifluoroacetic acid (2 ml). The resulting mixture was  
 stirred at room temperature for 2 hours. After  
 concentration under reduced pressure, diethyl ether was  
 added to the residue. The precipitate so formed was  
 collected by filtration, whereby the title compound (193  
 mg) was obtained as a colorless foam.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.96 (2H, br s), 3.08 (4H, br s), 3.27-  
 3.96 (6H, m), 4.37 (4H, br s), 7.70 (1H, dd, J=8.8, 2.0 Hz),  
 7.82 (1H, d, J=8.8 Hz), 8.20-8.28 (3H, m), 8.50 (1H, s).

MS (FAB) m/z: 535 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 537 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-130] N-[[2-[[4-(6-Chloronaphthalen-2-



yl)sulfonyl]piperazin-1-yl]carbonyl]-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-6-  
yl]acetyl]methanesulfonamide hydrochloride

In tetrahydrofuran (20 ml) was dissolved [2-[[4-[(6-  
5 chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl]acetic acid  
trifluoroacetate (110 mg), followed by the addition of  
carbonyldiimidazole (60 mg). The resulting mixture was  
heated under reflux for 1 hour. After the reaction was  
10 cooled to room temperature, methanesulfonamide (34 mg) and  
1,8-diazabicyclo[5.4.0]-7-undecene (0.05 ml) were added and  
they were stirred for 30 minutes. The reaction mixture was  
concentrated under reduced pressure. To the residue was  
added methylene chloride, followed by washing with water,  
15 0.2N hydrochloric acid and saturated aqueous NaCl solution,  
each once. The organic layer thus extracted was dried over  
anhydrous sodium sulfate and distilled under reduced  
pressure to remove the solvent. The residue was purified  
by chromatography on a silica gel column (methylene  
20 chloride : methanol = 100:4), whereby colorless foam was  
obtained. The resulting foam was suspended in a 1N aqueous  
hydrochloric acid in ethanol solution (1 ml), followed by  
concentration under reduced pressure and azeotropy with  
water, whereby the title compound (44 mg) was obtained as  
25 pale yellow foam.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.00(2H,br s), 3.11(4H,br s),

3.28 (3H, s), 3.32-4.06 (6H, m), 4.40 (4H, br s),  
 7.70 (1H, dd, J=8.8, 2.0 Hz), 7.82 (1H, d, J=8.8 Hz),  
 8.14 (1H, d, J=8.8 Hz), 8.22 (1H, s), 8.25 (1H, d, J=8.8 Hz),  
 8.50 (1H, s).

5 MS (FAB) m/z: 612 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 614 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-131] Ethyl [4-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]piperazin-1-yl]acetate hydrochloride

10 In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> at 100°C) δ: 1.26 (3H, t, J=7.2 Hz), 2.80-3.35 (13H, m), 3.44-3.89 (11H, m), 4.20 (2H, q, J=7.2 Hz),  
 4.52 (2H, br s), 7.67 (1H, dd, J=8.8, 1.7 Hz),

15 7.81 (1H, d, J=8.8, 1.7 Hz), 8.11 (1H, d, J=8.8 Hz), 8.16 (1H, s),  
 8.19 (1H, d, J=8.8 Hz), 8.47 (1H, s).

MS (FAB) m/z: 689 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 691 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-132] [4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]carbonyl]piperazin-1-yl]acetic acid hydrochloride

20

In the same manner as in Example B-23, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> at 100°C) δ: 2.84-2.93 (5H, m), 3.10-3.34 (7H, m), 3.45-3.61 (2H, m), 3.70-4.70 (12H, m),

25

7.67 (1H, dd, J=8.8, 2.0 Hz), 7.81 (1H, d, J=8.8, 1.7 Hz),  
 8.11 (1H, d, J=8.8 Hz), 8.17 (1H, s), 8.20 (1H, d, J=8.8 Hz),  
 8.48 (1H, s).

MS (FAB) m/z: 661 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 663 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example B-133] N-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-  
 1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazin-2-yl]carbonyl]methanesulfonamide  
 hydrochloride

In tetrahydrofuran (30 ml) was dissolved 2-carbamoyl-  
 10 4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine  
 (300 mg), followed by the addition of a 0.5 mole toluene  
 solution (1.12 ml) of potassium bis(trimethylsilyl)amide.  
 The resulting mixture was stirred for 10 minutes under ice  
 15 cooling. After the addition of methanesulfonyl chloride  
 (0.04 ml), the resulting mixture was warmed up to room  
 temperature and stirred for 1 hour. The reaction mixture  
 was concentrated under reduced pressure. Methylene  
 chloride was added to the residue and the resulting mixture  
 20 was washed once with water and once with saturated aqueous  
 NaCl solution. The organic layer thus extracted was dried  
 over anhydrous sodium sulfate and distilled under reduced  
 pressure to remove the solvent. The residue was purified  
 by chromatography on a silica gel column (methylene  
 25 chloride : methanol = 100:0 ~ 100:3), whereby colorless  
 foam was obtained. The resulting foam was suspended in 1N

hydrochloric acid (1 ml). The resulting suspension was concentrated under reduced pressure, whereby the title compound (96 mg) was obtained as pale yellow foam.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.73-2.84 (1H,m), 2.90 (6H,s), 3.09-  
 3.77 (8H,m), 3.99-4.27 (1H,m), 4.39-4.51 (1H,m), 4.69-  
 4.79 (1H,m), 4.99 (1H,s), 7.64-7.73 (2H,m), 8.06-8.10 (1H,m),  
 8.12-8.19 (1H,m), 8.44 (1H,s), 11.41 (1H,br s), 11.52 (1H,s).  
 MS (FAB) m/z: 612 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 614 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-134] 5-[2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]ethyl]tetrazole trifluoroacetate

In N,N-dimethylformamide (10 ml) were dissolved lithium 6-tert-butoxycarbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (329 mg),  
 5-[2-[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-2-yl]ethyl]tetrazole trifluoroacetate (295 mg), 1-hydroxybenzotriazole monohydrate (9 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (114 mg), followed by stirring overnight at room temperature.  
 The reaction mixture was concentrated under reduced pressure. Methylene chloride was added to the residue and the resulting mixture was washed with water and saturated aqueous NaCl solution, each once. The organic layer was then dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue

was purified by chromatography on a silica gel column (methylene chloride : methanol = 25:2), whereby pale yellow foam (48 mg) was obtained. The resulting foam was dissolved in methylene chloride (1 ml), followed by the addition of trifluoroacetic acid (1 ml). After concentration under reduced pressure, the precipitate so formed was collected by filtration while being washed with diethyl ether, whereby the title compound (48 mg) was obtained as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.12-1.40 (2H,m), 1.95-3.00 (7H,m), 3.42-3.47 (1H,m), 3.60-3.88 (2.5H,m), 4.10-4.15 (0.5H,br s), 4.38-4.45 (2H,m), 4.67-4.80 (1H,m), 5.25-5.31 (0.5H,m), 5.58-5.65 (0.5H,m), 7.70 (1H,d,J=8.8Hz), 7.82 (1H,d,J=8.8Hz), 8.14 (1H,d,J=8.8Hz), 8.18-8.26 (2H,m), 8.46-8.50 (1H,m).

MS (FAB) m/z: 573 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 575 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-135] 5-[2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]ethyl]tetrazole

In the same manner as in Example B-32, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.08-1.40 (2H,m), 1.90-3.84 (15.5H,m), 4.10 (0.5H,br s), 4.32-4.43 (0.5H,m), 4.72-4.80 (0.5H,m), 5.35-5.43 (0.5H,m), 5.69-5.80 (0.5H,m), 7.68 (1H,dd,J=8.8,2.0Hz).

MS (FAB) m/z: 587 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 589 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-136] 5-[[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)carbonyl]amino]methyl]tetrazole trifluoroacetate

5 In the same manner as in Example B-134, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.63-2.78 (1H,m), 2.85-2.93 (1H,m), 2.99-3.05 (1H,m), 3.28-3.79 (6H,m), 4.27-4.34 (1H,m), 4.40-4.70 (3.5H,m), 5.13-5.16 (0.5H,m), 5.48-5.56 (0.5H,m), 6.10-10 6.13 (0.5H,m), 7.70 (1H,d,J=8.8Hz), 7.79 (1H,d,J=8.8Hz), 8.08-8.26 (3H,m), 8.48 (1H,s), 8.89-9.00 (1H,m).

MS (FAB) m/z: 602 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 604 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-137] 5-[[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)carbonyl]amino]methyl]tetrazole

In the same manner as in Example B-32, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.36 (3H,s), 3.59 (1H,d,J=12.2Hz), 3.65-20 3.75 (1H,m), 4.16-4.56 (4.5H,m), 5.06 (0.5H,br s), 5.48-5.57 (0.5H,m), 6.20 (0.5H,br s), 7.67 (1H,dd,J=8.8,2.0Hz), 7.80 (1H,d,J=8.8Hz), 8.05-8.35 (4H,m), 8.49 (1H,s).

[Example B-138] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]methyl]-4,5-dihydro-5-oxo-1,3,4-oxadiazole trifluoroacetate

In the same manner as in Example B-134, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.38-2.69 (2H,m), 2.92-3.11 (3H,m), 3.18-3.34 (1H,m), 3.40-3.88 (5H,m), 4.39-4.47 (2.5H,m),  
 4.99 (0.5H,br s), 5.38-5.44 (0.5H,m), 5.72-5.88 (0.5H,br s),  
 7.70 (1H,d,J=8.8Hz), 7.81 (1H,d,J=8.8Hz), 8.15 (1H,d,J=8.8Hz),  
 8.22 (1H,s), 8.24 (1H,d,J=8.8Hz), 8.50 (1H,s), 9.23 (2H,br s),  
 12.03 (0.5H,s), 12.08 (0.5H,s).

MS (FAB) m/z: 575 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 577 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-139] 2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)methyl]-4,5-dihydro-5-oxo-1,3,4-oxadiazole

In the same manner as in Example B-32, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.35 (3H,s), 2.37-2.82 (6H,m), 2.97-3.36 (2.5H,m), 3.45-3.88 (4.5H,m), 4.40-4.46 (0.5H,m),  
 4.98 (0.5H,br s), 5.45-5.55 (0.5H,br s), 5.93 (0.5H,br s),  
 7.70 (1H,dd,J=8.8,2.0Hz), 7.81 (1H,dd,J=8.8,2.0Hz),  
 8.15 (1H,d,J=8.8Hz), 8.22 (1H,s), 8.24 (1H,d,J=8.8Hz),  
 8.50 (1H,s), 11.91-12.10 (1H,m).

MS (FAB) m/z: 589 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 591 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-140] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[[(morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

hydrochloride

In the same manner as in Example B-1, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.33-3.85 (19H,m), 4.35-4.50 (2.5H,m),  
 5.01-5.08 (0.5H,m), 5.27-5.37 (0.5H,m), 5.68-5.78 (0.5H,m),  
 7.03 (1H,s), 7.32 (1H,d,J=8.8Hz), 7.48 (1H,d,J=8.8Hz),  
 7.77 (1H,s), 9.54 (2H,br s), 12.45 (1H,s).

MS (FAB)  $m/z$ : 593  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 595  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example B-141] 1-[[6-(1-Acetoxyethoxy)carbonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl(morpholin-4-yl)carbonyl]methyl]piperazine

In ethanol (6 ml) was dissolved 4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methyl(morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride (200 mg), followed by the addition of diisopropylethylamine (83  $\mu\text{l}$ ) and 1-acetoxyethyl p-nitrophenyl carbonate (128 mg). The resulting mixture was stirred at room temperature for 5 hours. The solvent was distilled off under reduced pressure. Methylene chloride and an aqueous solution of sodium bicarbonate were added and the mixture was separated into layers. The organic layer was dried over anhydrous sodium sulfate and the filtrate was concentrated. The residue was purified by chromatography on a silica gel column (1-2% methanol - methylene chloride). The product



was dissolved in ethyl acetate, followed by crystallization from diethyl ether, whereby the title compound (100 mg) was obtained as colorless powder.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.43(3H,br s), 2.00-2.03(3H,m), 2.30-  
 5 3.80(19H,m), 4.35-4.45(0.5H,m), 4.61-4.77(2H,m), 5.01-  
 5.08(0.5H,m), 5.27-5.37(0.5H,m), 5.71-5.82(0.5H,m), 6.65-  
 6.68(1H,m), 7.01(1H,s), 7.30(1H,d,J=8.8Hz),  
 7.47(1H,d,J=8.8Hz), 7.75(1H,s), 12.40(1H,s).

MS (FAB) m/z: 723 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 725 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 [Example B-142] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

In the same manner as in Example B-62, the title compound was obtained.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.41(9H,s), 2.43-2.85(5H,m), 3.15-  
 3.75(6H,m), 4.20-4.27(1H,m), 4.40-4.48(0.5H,m), 4.60-  
 4.67(2H,m), 5.01(0.5H,s), 5.52-5.57(0.5H,m), 6.19(0.5H,br  
 s), 6.99-7.01(1H,m), 7.30(1H,d,J=8.8Hz), 7.44-7.48(1H,m),  
 7.76(1H,s), 8.04-8.12(1H,m), 12.39(1H,s).

20 MS (FAB) m/z: 623 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 625 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-143] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine hydrochloride

25 In the same manner as in Example B-1, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.43-2.75 (5H, m), 2.95 (1H, br s),  
 3.02 (1H, br s), 3.15-3.25 (0.5H, m), 3.38-3.50 (2H, m), 3.50-  
 3.62 (0.5H, m), 3.63-3.75 (1H, m), 4.20-4.27 (1H, m), 4.35-  
 4.50 (2.5H, m), 5.00 (0.5H, br s), 5.42-5.53 (0.5H, m),  
 5 6.15 (0.5H, br s), 7.01 (1H, s), 7.30 (1H, d, J=8.8Hz),  
 7.47 (1H, d, J=8.8Hz), 7.77 (1H, s), 8.09-8.14 (1H, m), 9.43 (1H, br  
 s), 12.42 (1H, s).

MS (FAB) m/z: 523 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 525 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-144] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-  
 10 hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

In methylene chloride (25 ml) were dissolved 4-[(5-  
 chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-  
 [(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 15 yl)carbonyl]piperazine (209 mg) and benzoyl peroxide (70%,  
 138 mg) at room temperature, followed by heating under  
 reflux for 9 hours. By the purification by chromatography  
 on a silica gel column (4% methanol - methylene chloride),  
 a crudely purified product of 1-[(6-benzoyloxy-4,5,6,7-  
 20 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-  
 chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine  
 (190 mg) was obtained as a colorless glassy solid. The  
 resulting solid was dissolved in a mixed solvent of  
 tetrahydrofuran (20 ml) and methanol (20 ml), followed by  
 25 the addition of a 1N aqueous solution (2.00 ml) of sodium  
 hydroxide. The resulting mixture was stirred at room

temperature for 10 minutes. The solvent was distilled off and the residue was separated into layers by the addition of chloroform and water. The organic layer was dried over anhydrous sodium sulfate and the filtrate was concentrated.

5 The residue was purified by preparative thin-layer chromatography (4% methanol - methylene chloride) using silica gel, whereby the title compound (19 mg) was obtained as colorless powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.75-3.25 (7H, m), 3.34 (2H, br s), 3.58-  
10 3.68 (1H, m), 4.05-4.45 (2H, br), 4.53-4.73 (2H, m), 5.25 (0.5H, br s), 5.50-5.75 (2.5H, m), 6.11 (0.5H, br s), 6.50 (0.5H, s), 7.05 (1H, br s), 7.25-7.32 (1H, m), 7.35-7.45 (1H, m), 7.64 (1H, s), 10.73 (1H, s).

HRMS (FAB) m/z: 539.0920 (M+H)<sup>+</sup> (calcd for C<sub>21</sub>H<sub>24</sub>ClN<sub>6</sub>O<sub>5</sub>S<sub>2</sub>,  
15 539.0938).

[Example B-145] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

20 In the same manner as in Example B-94, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.40-2.85 (7H, m), 2.89 (3H, s), 3.00-  
3.30 (3H, br), 3.40-3.82 (4H, m), 4.30-4.80 (2.5H, br),  
5.06 (0.5H, br s), 5.26-5.40 (0.5H, m), 5.81 (0.5H, br s),  
25 7.02 (1H, s), 7.31 (1H, d, J=8.6Hz), 7.48 (1H, d, J=8.6Hz), 7.76 (1H, s), 7.89-7.94 (1H, m), 11.16 (1H, br s), 12.44 (1H, s).

MS (FAB) m/z: 551 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 553 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-146] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-  
[(methoxycarbonyl)methyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 In the same manner as in Example B-62, the title  
compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.49(3H,s), 2.50-2.90(7H,m), 2.95-  
3.06(1H,m), 3.10-3.25(0.5H,m), 3.35-3.50(0.5H,m), 3.50-  
3.70(5H,m), 3.70-3.95(2H,br), 4.60-4.64(0.5H,br),  
10 5.22(0.5H,br s), 5.71-5.75(0.5H,m), 6.18(0.5H,br s),  
6.96(1H,s), 7.31(1H,dd,J=8.8,1.7Hz), 7.36(1H,d,J=8.8Hz),  
7.65(1H,d,J=1.7Hz), 9.15-9.20(1H,br).

MS (FAB) m/z: 552 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 554 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-147] 2-(Carboxymethyl)-4-[(5-chloroindol-2-  
15 yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-77, the title  
compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.38(3H,s), 2.40-3.81(13H,m), 4.36-  
20 4.41(0.5H,br), 5.01(0.5H,br s), 5.41-5.44(0.5H,m),  
5.86(0.5H,br s), 7.03(1H,s), 7.31(1H,dd,J=8.8,1.7Hz),  
7.47(1H,d,J=8.8Hz), 7.76(1H,d,J=1.7Hz), 12.42(1H,s).

MS (FAB) m/z: 538 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 540 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-148] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-  
25 [(1,3-dioxolan-2-yl)methyl]carbamoyl]methyl]-1-[(6-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

In the same manner as in Example B-79, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.50 (3H, s), 2.51-3.10 (7H, m), 3.30-3.65 (3H, m), 3.68 (2H, s), 3.70-4.12 (6H, m), 4.46-4.57 (0.5H, m), 4.90-5.00 (1H, m), 5.10-5.20 (0.5H, m), 5.55-5.70 (0.5H, m), 5.87 (0.5H, s), 6.28 (0.5H, s), 6.52 (0.5H, s), 6.99 (1H, s), 7.28 (1H, d,  $J=8.8\text{Hz}$ ), 7.37 (1H, d,  $J=8.8\text{Hz}$ ), 7.64 (1H, s),  
10 10.38 (0.5H, br s), 10.62 (0.5H, s).

MS (FAB)  $m/z$ : 623  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 625  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example B-149] 1-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl)acetyl]piperidin-4-one  
15 ethyleneketal

In the same manner as in Example B-79, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.60 (4H, s), 2.49 (3H, s), 2.55-3.20 (7H, m), 3.20-3.35 (0.5H, m), 3.50-3.85 (8H, m), 4.00 (5H, br s), 4.12-  
20 4.23 (0.5H, m), 4.55-4.67 (0.5H, m), 4.95-5.07 (0.5H, m), 5.45-5.60 (0.5H, m), 5.95-6.07 (0.5H, m), 7.00 (1H, s), 7.22-7.31 (1H, m), 7.37 (1H, d,  $J=8.8\text{Hz}$ ), 7.64 (1H, s), 10.37 (0.5H, br s), 11.14 (0.5H, s).

MS (FAB)  $m/z$ : 663  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 665  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

25 [Example B-150] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N,N-

dimethylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-79, the title  
5 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.40-2.80(6H,m), 2.81-3.20(9H,m), 3.35-3.85(5H,m), 4.30-4.80(2.5H,br), 5.00(0.5H,br s), 5.26-5.40(0.5H,m), 5.75(0.5H,br s), 7.01(1H,s), 7.30(1H,d,J=8.6Hz), 7.47(1H,d,J=8.6Hz), 7.75(1H,s),  
10 11.22(1H,br s), 12.42(1H,s).

MS (FAB) m/z: 565 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 567 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-151] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(2,2-diethoxyethyl)carbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 In the same manner as in Example B-79, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.15-1.27(6H,m), 2.50(3H,s), 2.55-3.10(8H,m), 3.30-3.90(10H,m), 4.00-4.15(1H,m), 4.45-4.60(1.5H,m), 5.12(0.5H,br s), 5.55-5.70(0.5H,m),  
20 5.82(0.5H,br s), 6.19(0.5H,br s), 6.59(0.5H,br s), 7.01(1H,s), 7.22-7.31(1H,m), 7.36(1H,d,J=9.0Hz), 7.65(1H,s), 10.21(0.5H,br s), 10.72(0.5H,s).

MS (FAB) m/z: 653 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 655 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-152] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
25

yl)carbonyl]-2-[[N-(  
(tetrahydrofurfuryl)carbamoyl)methyl]piperazine  
hydrochloride

In the same manner as in Example B-62, the title  
5 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.40-1.55 (1H,m), 1.65-1.90 (3H,m), 2.40-  
2.89 (3H,br), 2.90 (3H,s), 3.00-3.40 (5H,m), 3.41-3.85 (9H,m),  
4.25-4.70 (1.5H,m), 5.08 (0.5H,br s), 5.26-5.37 (0.5H,m),  
5.83 (0.5H,br s), 7.03 (1H,s), 7.31 (1H,d,J=9.0Hz),  
10 7.48 (1H,d,J=9.0Hz), 7.77 (1H,s), 8.07 (1H,br s), 11.00-  
11.30 (1H,br), 12.43 (1H,s).

MS (FAB) m/z: 621 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 623 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-153] 1-[[6-(tert-Butoxycarbonylaminosulfonyl)-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-  
15 [(5-chloroindol-2-yl)sulfonyl]-2-[[ (morpholin-4-  
yl)carbonyl]methyl]piperazine

To methylene chloride (3 ml) was added tert-butyl  
alcohol (53 mg). While cooling to 0°C,  
chlorosulfonylisocyanate (88 mg) was added to the resulting  
20 mixture, followed by stirring for 10 minutes. To the  
reaction mixture was added a solution of 4-[(5-chloroindol-  
2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-  
[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]]piperazine (300 mg) and triethylamine (475 mg)  
25 in methylene chloride (3 ml). After stirring at room  
temperature for 1 hour, water was added to the reaction

mixture and the resulting mixture was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography (methanol : methylene chloride = 1:19) using as a carrier silica gel, whereby the title compound (311 mg) was obtained. A portion of the compound was purified further by preparative thin-layer chromatography (methanol : methylene chloride = 1:9) using silica gel, followed by the addition of ether. The instrumental data on the resulting pale yellow solid was as follows:

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.23, 1.24 (total 9H, each s), 2.33-3.75 (19H, m), 4.37-5.86 (4H, m), 7.03 (1H, s), 7.31 (1H, d,  $J=8.8\text{Hz}$ ), 7.47 (1H, d,  $J=8.8\text{Hz}$ ), 7.76 (1H, s), 11.21 (1H, s), 12.42 (1H, s).

MS (FAB)  $m/z$ : 772 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-154] 1-[[6-(Aminosulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine

In methylene chloride (3 ml) was dissolved 1-[[6-(tert-butoxycarbonylaminosulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine (275 mg), followed by the



addition of trifluoroacetic acid (3 ml). The resulting mixture was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure. A saturated solution of hydrochloride in ethanol (3 ml) was added and the resulting mixture was stirred at room temperature for 1.5 hours. The residue obtained by distilling off the solvent under reduced pressure was added with methylene chloride and water to separate into layers. The water layer was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (methanol : methylene chloride = 1:9) using silica gel. The solid thus obtained was dissolved in a small amount of methylene chloride, followed by solidification by the addition of diethyl ether, whereby the title compound (50 mg) was obtained as a pale yellow solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.33-3.75 (19H,m), 4.35-5.84 (4H,m), 7.01-7.02 (3H,m), 7.31 (1H,d,J=8.8Hz), 7.48 (1H,d,J=9.0Hz), 7.76 (1H,s), 12.41 (1H,s).

MS (FAB)  $m/z$ : 672 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-155] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-[6-[phenylsulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

In the same manner as in Example B-95, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.33-3.74 (19H,m), 4.34-5.71 (4H,m),  
7.02 (1H,s), 7.31 (1H,d,J=8.6Hz), 7.47 (1H,d,J=9.0Hz), 7.57-  
5 7.61 (2H,m), 7.65-7.67 (1H,m), 7.76 (1H,s),  
7.80 (2H,d,J=7.8Hz), 12.40 (1H,s).

HRMS (FAB) m/z: 733.1333 (M+H)<sup>+</sup> (calcd for C<sub>31</sub>H<sub>33</sub>ClN<sub>6</sub>O<sub>7</sub>S<sub>3</sub>,  
733.1340).

[Example B-156] 5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
10 c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-  
2-(N-methylcarbamoyl)-1-[[6-(tert-butoxycarbonyl)piperazine

In diethyl ether (8 ml) dried by a molecular sieve was  
dissolved 6-(tert-butoxycarbonyl)-5-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridine (203 mg). After the  
15 container employed was purged with argon, the temperature  
was cooled to -78°C. To the resulting solution, n-butyl  
lithium (a 1.66 mole n-hexane solution, 506 μl) was added  
dropwise, followed by stirring at the same temperature for  
1.5 hours. While a carbon dioxide gas was blown into the  
20 reaction mixture, the mixture was stirred at the same  
temperature for 1 hour. After warming up to room  
temperature, the solvent was distilled off under reduced  
pressure, whereby crude lithium 6-(tert-butoxycarbonyl)-5-  
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-  
25 carboxylate was obtained. This product was provided for  
the subsequent reaction without purification. In N,N-

dimethylformamide (4 ml) was dissolved 3-(N-methylcarbamoyl)-1-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]piperazine (248 mg), followed by the addition of the crude lithium 6-(tert-butoxycarbonyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (ca. 550  $\mu$ mol), which had been obtained above, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (144 mg) and 1-hydroxybenzotriazole (34 mg). The resulting mixture was stirred overnight at room temperature. Methylene chloride was added to the reaction mixture. The resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by flash column chromatography (hexane : ethyl acetate = 2:1) using as a carrier silica gel, whereby the title compound (121 mg) was obtained as a white solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.12-1.17 (3H, m), 1.49 (9H, s), 2.62-3.23 (7H, m), 3.63 (1H, d,  $J=12.3\text{Hz}$ ), 4.22 (1H, d,  $J=17.9\text{Hz}$ ), 4.55-4.74 (2H, m), 4.83-4.89 (1H, m), 5.09-5.16 (1H, m), 5.25-6.49 (2H, m), 7.06 (1H, s), 7.27-7.30 (2H, m), 7.38-7.42 (1H, m), 7.64 (1H, s), 10.62-10.67 (1H, m).

[Example B-157] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.39-1.40 (3H,m), 2.32-3.68 (10H,m),  
4.21-5.00 (4H,m), 5.44-6.15 (1H,m), 7.01 (1H,s),  
5 7.31 (1H,dd,  $J=8.5, 2.0\text{Hz}$ ), 7.48 (1H,d,  $J=8.5\text{Hz}$ ), 7.77 (1H,s),  
8.11-8.14 (1H,m), 9.38-9.75 (2H,m), 12.42 (1H,s).  
 $\text{HRMS}$  (FAB)  $m/z$ : 537.1140 ( $\text{M}+\text{H}$ ) $^+$  (calcd for  $\text{C}_{22}\text{H}_{26}\text{N}_6\text{O}_4\text{ClS}_2$ ,  
537.1145).

[Example B-158] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(5,6-  
10 dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-2-(N-methylcarbamoyl)piperazine hydrochloride

In a saturated solution of hydrochloride in ethanol (2  
ml) was dissolved 1-[[6-(tert-butoxycarbonyl)-5-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]-4-  
15 [(5-chloroindol-2-yl)sulfonyl]-2-(N-  
methylcarbamoyl)piperazine (40 mg), followed by stirring at  
room temperature for 1 hour. Diethyl ether was added to  
the reaction mixture. The precipitate so formed was  
collected by filtration and washed with diethyl ether.  
20 Methylene chloride (7 ml) and triethylamine (81  $\mu\text{l}$ ) were  
added, followed by the addition of acetic acid (34  $\mu\text{l}$ ). To  
the resulting mixture were added a 30% aqueous solution (21  
 $\mu\text{l}$ ) of formaldehyde and sodium triacetoxyborohydride (64  
mg), followed by stirring at room temperature for 30  
25 minutes. The solvent was distilled off under reduced  
pressure. Methylene chloride was added and the resulting

mixture was washed with water and saturated aqueous NaCl  
 solution. The organic layer was dried over anhydrous  
 sodium sulfate and distilled under reduced pressure to  
 remove the solvent. The residue was dissolved in a 1N  
 5 ethanol hydrochloride solution. After stirring at room  
 temperature for 5 minutes, the solvent was distilled off  
 under reduced pressure. The precipitate so formed was  
 collected by filtration and washed with diethyl ether,  
 whereby the title compound (68 mg) was obtained as a white  
 10 solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.32-1.40 (3H,m), 2.33-3.94 (13H,m),  
 4.23-4.26 (1H,m), 4.44-5.01 (3H,m), 5.50-6.16 (1H,m),  
 7.02 (1H,s), 7.31 (1H,dd,J=8.8,2.0Hz), 7.48 (1H,d,J=8.8Hz),  
 7.77 (1H,s), 8.10-8.16 (1H,m), 11.15-11.54 (1H,m),  
 15 12.43 (1H,s).

[Example B-159] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
 (N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrooxazolo[5,4-  
 c]pyridin-2-yl)carbonyl]piperazine trifluoroacetate

To a solution of 6-(tert-butoxycarbonyl)-2-  
 20 methoxycarbonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine  
 (120 mg) in tetrahydrofuran (4.0 ml) were added water (1.0  
 ml) and lithium hydroxide (18.0 mg) at room temperature.  
 After stirring for 10 minutes, the solvent was distilled  
 off under reduced pressure. To a solution of the residue  
 25 in N,N-dimethylformamide were added 1-[(6-chloronaphthalen-  
 2-yl)sulfonyl]-3-(N-methylcarbamoyl)piperazine

hydrochloride (190 mg), 1-hydroxybenzotriazole monohydrate (11.5 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (90.0 mg) at room temperature. After stirring for 4 hours, methylene chloride (30 ml) and water (250 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (20 ml). The organic layers were combined, washed with a saturated aqueous solution (50 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 25 g, methylene chloride : acetone = 5:1 → 3:1), whereby a colorless transparent oil was obtained. To a solution of the resulting substance in methylene chloride (4.0 ml) was added trifluoroacetic acid (4.0 ml) at room temperature and the resulting mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was reprecipitated from a methylene chloride - methanol - diethyl ether system, whereby the title compound (165 mg) was obtained as a pale brown solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.30-2.70 (2H,m), 2.58 (3H,d,J=3.9Hz), 2.77 (2H,br d,J=16.1Hz), 3.05-3.60 (3H,m), 3.71 (1H,br d,J=11.2Hz), 4.29 (1H,br d,J=11.7Hz), 4.35-4.50 (2H + 1/2 of 1H,m), 4.96 (1/2 of 1H,br s), 5.05 (1/2 of 1H,br d,J=13.2Hz), 5.78 (1/2 of 1H,br s), 7.71 (1H,d,J=8.3Hz), 7.73-7.83 (1H,m), 8.00-8.20 (1H,m), 8.15 (1H,d,J=8.3Hz), 8.24 (1H,s),

8.25 (1H, d, J=8.3 Hz), 8.48 (1/2 of 1H, s), 8.49 (1/2 of 1H, s),  
9.34 (2H, br s).

MS (FAB) m/z: 518 (M+H)<sup>+</sup>.

[Example B-160] 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
5 (N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-  
tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-32, the title  
compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.48 (3H, s), 2.52-2.80 (6H, m), 2.80-  
10 3.00 (3H, m), 3.10 (1/2 of 1H, t, J=11.2 Hz), 3.49 (1/2 of  
1H, t, J=11.2 Hz), 3.54 (2H, s), 3.78 (1/2 of 1H, br d, J=10.3 Hz),  
3.86 (1/2 of 1H, br d, J=11.2 Hz), 4.45 (1H, t, J=11.4 Hz),  
4.63 (1/2 of 1H, br d, J=12.7 Hz), 5.24 (1/2 of 1H, s), 5.38 (1/2  
of 1H, br d, J=12.7 Hz), 6.12 (1/2 of 1H, br s), 6.16 (1/2 of  
15 1H, s), 6.40 (1/2 of 1H, br s), 7.58 (1H, d, J=7.8 Hz),  
7.80 (1H, d, J=7.8 Hz), 7.86-7.96 (3H, m), 8.34 (1H, s).

MS (FAB) m/z: 532 (M+H)<sup>+</sup>.

[Example B-161] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-  
tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-  
20 chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-62, the title  
compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.46 (9H, s), 2.64 (2H, br s), 3.22 (4H, br s),  
3.71 (2H, br s), 3.90 (2H, br s), 4.42 (2H, br s), 4.53 (2H, br s),  
25 6.97 (1H, d, J=2.0 Hz), 7.33 (1H, dd, J=8.8, 2.0 Hz),

7.37 (1H, d, J=8.8Hz), 7.67 (1H, s), 8.71 (1H, br s).

[Example B-162] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[methylpiperazine

5 yl)carbonyl]methyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 (9H, s), 2.50-2.70 (2H, m), 2.70-3.20 (2H + 1/2 of 1H, m), 3.38 (1/2 of 1H, t, J=11.2Hz), 3.50-3.95 (11H + 1/2 of 1H, m), 3.99 (1/2 of 1H, br d, J=12.7Hz), 4.40-4.60 (1/2 of 1H, br), 4.53 (2H, s), 4.64 (1/2 of 1H, br d, J=13.7Hz), 5.02 (1/2 of 1H, br s), 5.24 (1/2 of 1H, br s), 5.79 (1/2 of 1H, br s), 7.00 (1H, s), 7.20-7.35 (1H, m), 7.38 (1H, d, J=8.8Hz), 7.65 (1/2 of 1H, s), 7.67 (1/2 of 1H, s), 9.89 (1/2 of 1H, br s), 10.60-11.00 (1/2 of 1H, br).

[Example B-163] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

To a solution of 1-[[6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (100 mg) in methylene chloride (3.0 ml) was added trifluoroacetic acid (3.0 ml) at room temperature, followed by stirring for 15 minutes. The reaction mixture was concentrated under reduced pressure. To the residue were added methylene chloride (4.0 ml), triethylamine (50.0 μl), acetic acid (21.0 μl),



formalin (23.5  $\mu$ l) and sodium triacetoxyborohydride (58.0 mg) at room temperature. After stirring for 1 hour, methylene chloride (20 ml) and a saturated aqueous solution (50 ml) of sodium bicarbonate were added to the reaction mixture to separate it into layers. The water layer was extracted with methylene chloride (20 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by preparative thin-layer chromatography (chloroform : methanol = 10:1) using silica gel, whereby the free form (82.6 mg) of the title compound was obtained as a colorless solid. To the resulting compound were added a 1N aqueous solution of hydrochloric acid, tetrahydrofuran and methanol, followed by concentration under reduced pressure, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.90(4H,s), 3.11(3H,br s), 3.25-3.75(2H,br), 3.35(2H,s), 3.75(2H,br s), 4.16(2H,br s), 4.20-4.75(2H,br), 7.04(1H,s), 7.32(1H,dd,J=8.8,1.0Hz), 7.50(1H,d,J=8.8Hz), 7.78(1H,d,J=1.0Hz), 11.51(1H,br s), 12.46(1H,s).

MS (FAB)  $m/z$ : 464 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-164] 4-(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine hydrochloride

In the same manner as in Example B-163, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.30-2.75 (2H,m), 2.75-3.20 (2H,m),  
2.90 (3H,s), 3.20-3.90 (15H,m), 4.30-4.45 (1H + 1/2 of 1H,m),  
5 4.55-4.70 (1H,m), 4.89 (1/2 of 1H,br s), 5.05 (1/2 of 1H,br  
s), 5.47 (1/2 of 1H,br s), 7.04 (1H,s), 7.29-7.35 (1H,m),  
7.50 (1H,dd,J=8.8,2.9Hz), 7.76-7.80 (1H,m), 11.45-  
11.95 (1H,br), 12.49 (1H,br s).

MS (FAB) m/z: 591 (M+H)<sup>+</sup>.

10 [Example B-165] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-  
tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(6-  
chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

To a solution of lithium 6-(tert-butoxycarbonyl)-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate  
15 (70.0 mg) in N,N-dimethylformamide (4.0 ml) were added 1-  
[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine  
hydrochloride (90.0 mg), 1-hydroxybenzotriazole monohydrate  
(7.0 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
(64.0 mg) at room temperature. After stirring for 2 days,  
20 ethyl acetate (30 ml) and water (500 ml) were added to the  
reaction mixture to separate it into layers. The water  
layer was extracted with ethyl acetate (30 ml). The  
organic layers were combined, washed with a saturated  
aqueous solution of sodium bicarbonate (100 ml), dried over  
25 anhydrous sodium sulfate and distilled under reduced  
pressure to remove the solvent. The residue was purified

by preparative thin-layer chromatography (hexane : ethyl acetate = 1:1) using silica gel, whereby the title compound (37.9 mg) was obtained as a colorless transparent glassy substance.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47(9H,s), 2.65(2H,s),  
3.27(4H,t,J=5.0Hz), 3.70(2H,s), 3.91(2H,s), 4.42(2H,s),  
4.53(2H,s), 7.45(1H,dd,J=8.8,1.5Hz), 7.77(1H,s),  
7.81(1H,d,J=8.8Hz), 7.86(1H,d,J=1.5Hz).

MS (FAB)  $m/z$ : 567 (M+H) $^+$ .

10 [Example B-166] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-163, the title compound was obtained.

15  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.90(3H,s), 2.94(1H,br s), 3.10-  
3.25(4H,m), 3.49(2H,s), 3.64(1H,br s), 3.79(2H,s),  
4.21(2H,s), 4.39(1H,br s), 4.60(1H,br s),  
7.58(1H,dd,J=8.8,2.0Hz), 8.07(1H,d,J=8.8Hz), 8.10(1H,s),  
8.34(1H,d,J=2.0Hz), 11.70(1H,br s).

20 MS (FAB)  $m/z$ : 481 (M+H) $^+$ .

[Example B-167] 1-[(6-Methyl-4,5,6,7-  
tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(1-  
phenylsulfonyl-5-trimethylsilylethynylindol-2-  
yl)sulfonyl]piperazine

25 In the same manner as in Example B-103, the title

compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.25 (9H, s), 2.51 (3H, s),  
 2.69 (2H, t, J=5.4Hz), 2.78 (2H, t, J=5.4Hz), 3.52 (2H, br s),  
 3.55 (2H, br s), 3.59 (2H, s), 3.89 (2H, br s), 4.41 (2H, br s),  
 5 7.42 (2H, t, J=7.6Hz), 7.47 (1H, s), 7.55 (1H, t, J=7.6Hz),  
 7.59 (1H, dd, J=8.8, 1.7Hz), 7.69 (1H, d, J=1.7Hz),  
 8.00 (2H, d, J=7.6Hz), 8.22 (1H, d, J=8.8Hz).

[Example B-168] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 10

In the same manner as in Example B-104, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.48 (3H, s), 2.66 (2H, t, J=5.4Hz),  
 2.75 (2H, t, J=5.4Hz), 3.04 (1H, s), 3.21 (4H, t, J=4.4Hz),  
 15 3.54 (2H, s), 3.89 (2H, br s), 4.43 (2H, br s), 7.00 (1H, s),  
 7.37 (1H, d, J=8.6Hz), 7.47 (1H, dd, J=8.6, 1.5Hz), 7.86 (1H, br s),  
 8.85 (1H, br s).

MS (FAB/glycerol) m/z: 454 (M+H)<sup>+</sup>.

[Example B-169] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-ethylpiperazine  
 20

In the same manner as in Example B-165, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.90 (1/2 of 3H, t, J=7.1Hz), 0.96 (1/2 of  
 25 3H, t, J=7.1Hz), 1.47 (9H, s), 1.78-2.03 (2H, m), 2.45-

2.73(4H,m), 3.18(1/2 of 1H,t,J=11.5Hz), 3.51(1/2 of  
 1H,t,J=11.5Hz), 3.60-3.92(4H,m), 4.52(2H,s), 4.62(1/2 of  
 1H,d,J=13.0Hz), 4.79(1/2 of 1H,br s), 5.20(1/2 of 1H,br s),  
 5.40(1/2 of 1H,br s), 6.94(1H,d,J=1.5Hz),  
 5 7.31(1H,dd,J=8.8,2.0Hz), 7.37(1H,d,J=8.8Hz),  
 7.66(1H,d,J=2.0Hz), 8.87(1H,br s).

MS (FAB) m/z: 578 (M+H)<sup>+</sup>.

[Example B-170] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethyl-  
 1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 10 yl)carbonyl]piperazine trifluoroacetate

To a solution of 1-[[6-(tert-butoxycarbonyl)-4,5,6,7-  
 tetrahydrooxazolo[5,4-c]pyridin-2-yl]carbonyl]-4-[(5-  
 chloroindol-2-yl)sulfonyl]-2-ethylpiperazine (320 mg) in  
 methylene chloride (5.0 ml) was added trifluoroacetic acid  
 15 (5.0 ml) at room temperature, followed by stirring for 10  
 minutes. The reaction mixture was concentrated under  
 reduced pressure, whereby the title compound (423 mg) was  
 obtained as a pale brown solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.78(1/2 of 3H,t,J=6.9Hz), 0.83(1/2 of  
 20 3H,t,J=6.9Hz), 1.47(9H,s), 1.65-1.95(2H,m), 2.30-  
 2.70(2H,m), 2.80(2H,s), 3.13(1/2 of 1H,t,J=12.7Hz), 3.37-  
 4.00(2H + 1/2 of 1H,m), 3.42(2H,s), 4.30-4.47(2H + 1/2 of  
 1H,m), 4.60(1/2 of 1H,br s), 4.73(1/2 of 1H,d,J=14.0Hz),  
 4.91(1/2 of 1H,br s), 8.01(1H,s), 7.30(1H,d,J=8.8Hz),  
 25 7.47(1H,d,J=8.8Hz), 7.76(1H,s), 9.36(2H,br s), 12.42(1H,s).

MS (FAB) m/z: 478 (M+H)<sup>+</sup>.

[Example B-171] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-ethyl-  
1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-32, the title  
5 compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.73-0.83(3H,m), 1.60-1.92(2H,m), 2.30-  
2.70(2H,m), 2.75-3.03(2H,m), 2.89(3H,s), 3.03-3.53(2H + 1/2  
of 1H,m), 3.53-3.80(2H + 1/2 of 1H,m), 4.20-4.45(1H + 1/2  
of 1H,br), 4.60(1H + 1/2 of 1H,br s), 4.76(1/2 of  
10 1H,d,J=13.0Hz), 4.92(1/2 of 1H,br s), 7.00(1H,s),  
7.30(1H,dd,J=8.8,2.0Hz), 7.47(1H,d,J=8.8Hz),  
7.75(1H,d,J=2.0Hz), 11.57(1H,br s), 12.43(1H,s).

MS (FAB) m/z: 492 (M+H)<sup>+</sup>.

[Example B-172] 1-[[6-(tert-Butoxycarbonyl)-5,6,7,8-  
15 tetrahydropyrido[4,3-d]pyrimidin-2-yl]carbonyl]-4-[(5-  
chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-159, the title  
compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.49(9H,s), 2.96(2H,t,J=5.9Hz),  
20 3.14(2H,t,J=5.0Hz), 3.27(2H,t,J=5.1Hz), 3.53(2H,t,J=5.0Hz),  
3.75(2H,t,J=5.9Hz), 3.93(2H,t,J=5.1Hz), 4.62(2H,s),  
6.96(1H,s), 7.35(1H,dd,J=8.5,1.7Hz), 7.38(1H,d,J=8.5Hz),  
7.69(1H,d,J=1.7Hz), 8.48(1H,s), 8.77(1H,br s).

MS (FAB) m/z: 561 (M+H)<sup>+</sup>.

[Example B-173] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-

[(5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)carbonyl]piperazine trifluoroacetate

In the same manner as in Example B-170, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.96(2H,t,J=4.5Hz), 3.03(2H,t,J=6.0Hz),  
 3.11(2H,t,J=4.5Hz), 3.29(2H,t,J=4.5Hz), 3.49(2H,br s),  
 3.75(2H,t,J=4.5Hz), 4.36(2H,s), 7.03(1H,s),  
 7.32(1H,dd,J=8.8,1.7Hz), 7.49(1H,d,J=8.8Hz),  
 7.78(1H,d,J=1.7Hz), 8.70(1H,s), 9.25(2H,br s), 12.46(1H,s).  
 10 MS (FAB)  $m/z$ : 461 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-174] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)carbonyl]piperazine hydrochloride

15 In the same manner as in Example B-32, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.92(3H,s), 2.98(2H,br s), 3.06(1H,br s),  
 3.13(2H,t,J=5.0Hz), 3.28(1H,br s), 3.32(2H,t,J=5.0Hz),  
 3.46(1H,br s), 3.70(1H,br s), 3.77(2H,br s), 4.34(1H,br d,J=15.4Hz),  
 4.57(1H,br d,J=15.4Hz), 7.04(1H,d,J=1.6Hz),  
 20 7.34(1H,dd,J=8.8,2.0Hz), 7.62(1H,d,J=8.8Hz),  
 7.79(1H,d,J=2.0Hz), 8.71(1H,s), 11.67(1H,br s),  
 12.50(1H,d,J=1.6Hz).  
 MS (FAB)  $m/z$ : 475 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-175] 1-[[6-(tert-Butoxycarbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl]carbonyl]-4-[(5-

25

chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

In the same manner as in Example B-159, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.49(1/2 of 9H,s), 1.50(1/2 of 9H,s),  
 5 2.60-2.72(1/2 of 1H,m), 2.85-3.12(6H,m), 3.12-3.30(1H,m),  
 3.45-3.70(1H,m), 3.70-3.90(2H + 1/2 of 1H,m), 4.32(1/2 of  
 1H,br s), 4.60-4.75(1/2 of 1H + 2H,m), 4.81(1/2 of  
 1H,d,J=12.9Hz), 5.31-5.35(1/2 of 1H,m), 6.68(1/2 of 1H,br  
 s), 7.04(1/2 of 1H,s), 7.07(1/2 of 1H,s), 7.20-7.35(1H,m),  
 10 7.39(1/2 of 1H,d,J=8.8Hz), 7.40(1/2 of 1H,d,J=8.3Hz),  
 7.62(1/2 of 1H,s), 7.66(1/2 of 1H,s), 7.87(1/2 of 1H,br s),  
 10.47(1/2 of 1H,br s), 10.70(1/2 of 1H,br s).

MS (FAB) m/z: 618 (M+H)<sup>+</sup>.

[Example B-176] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-  
 15 methylcarbamoyl)-1-[(5,6,7,8-tetrahydropyrido[4,3-  
 d]pyrimidin-2-yl)carbonyl]piperazine trifluoroacetate

In the same manner as in Example B-170, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.30-2.58(2H,m), 2.60(1/2 of  
 20 3H,d,J=4.4Hz), 2.64(1/2 of 3H,d,J=4.2Hz), 2.65-2.75(1H,m),  
 3.00(1/2 of 2H,t,J=5.4Hz), 3.06(1/2 of 2H,t,J=6.2Hz),  
 3.29(1/2 of 1H,br t,J=11.0Hz), 3.39(1/2 of 1H,br  
 d,J=13.5Hz), 3.50(2H,br s), 3.53-3.80(1/2 of 1H + 1H,m),  
 4.10-4.30(1/2 of 1H,m), 4.35(1/2 of 2H,s), 4.38(1/2 of  
 25 2H,s), 4.50(1/2 of 1H,br d,J=13.5Hz), 5.05(1/2 of 1H,br s),  
 7.00(1/2 of 1H,s), 7.01(1/2 of 1H,s), 7.28-7.38(1H,m),



7.48 (1/2 of 1H, d, J=8.8Hz), 7.49 (1/2 of 1H, d, J=8.8Hz),  
 7.77 (1/2 of 1H, d, J=1.7Hz), 7.78 (1/2 of 1H, d, J=1.7Hz), 7.90-  
 8.03 (1/2 of 1H, m), 8.07-8.17 (1/2 of 1H, m), 8.69 (1/2 of  
 1H, s), 8.73 (1/2 of 1H, s), 9.24 (2H, br s), 12.43 (1H, s).

5 MS (FAB) m/z: 518 (M+H)<sup>+</sup>.

[Example B-177] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-32, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.30-2.55 (2H, m), 2.61 (1/2 of  
 3H, d, J=3.5Hz), 2.65 (1/2 of 3H, d, J=4.2Hz), 2.68-2.77 (1H, m),  
 2.93 (3H, br s), 2.97-3.18 (1H, m), 3.20-3.80 (6H, m), 4.04-  
 4.65 (3H, m), 5.07 (1/2 of 1H, br s), 7.00 (1/2 of  
 15 1H, d, J=1.5Hz), 7.02 (1/2 of 1H, d, J=1.7Hz), 7.30-7.37 (1H, m),  
 7.50 (1/2 of 1H, d, J=8.8Hz), 7.51 (1/2 of 1H, d, J=8.8Hz),  
 7.78 (1/2 of 1H, d, J=1.7Hz), 7.80 (1/2 of 1H, d, J=2.0Hz),  
 8.05 (1/2 of 1H, br s), 8.15 (1/2 of 1H, br d, J=4.2Hz),  
 8.70 (1/2 of 1H, s), 8.74 (1/2 of 1H, s), 11.68 (1H, br s),  
 20 12.48 (1H, s).

MS (FAB) m/z: 532 (M+H)<sup>+</sup>.

[Example B-178] 4-(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(piperidin-1-yl)ethyl]piperazine  
 25 hydrochloride

In the same manner as in Example B-62, the title

compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.16-3.79 (26H,m), 4.37-4.45 (1H,m),  
4.68-4.75 (2H,m), 5.40-5.47 (1H,m), 7.02 (1H,d,J=5.1Hz),  
7.32 (1H,dd,J=2.2,8.8Hz), 7.49 (1H,d,J=8.8Hz), 7.77 (1H,s).

5 MS (FAB)  $m/z$ : 591  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 593  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example B-179] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-[N-(2-methoxyethyl)amino]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-62, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.33-4.77 (21H,m), 3.29 (3H,s),  
3.34 (3H,s), 5.39-5.43 (1H,m), 7.01 (1H,d,J=4.4Hz),  
7.30 (1H,dd,J=7.8,2.0Hz), 7.49 (1H,d,J=8.8Hz), 7.76 (1H,s).

15 MS (FAB)  $m/z$ : 581  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 583  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example B-180] 1-[[6-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[2-(piperidin-1-yl)ethyl]piperazine

20 In the same manner as in Example B-62, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48 (9H,s), 1.16-3.79 (23H,m), 4.45-  
4.59 (1H,m), 4.65-4.75 (2H,m), 6.70-6.80 (1H,m), 6.96 (1H,s),  
7.28-7.31 (1H,m), 7.64 (1H,d,J=1.7Hz), 8.02 (1H,s).

25 MS (FAB)  $m/z$ : 677  $(\text{M}+\text{H})^+$ .

[Example B-181] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(piperidin-1-yl)ethyl]piperazine

In the same manner as in Example B-95, the title  
5 compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.54-3.83(23H,m), 2.89(3H,s), 4.59(2H,s),  
4.55-4.84(1H,m), 5.61-5.84(1H,m), 7.00(1H,d,J=15.0Hz),  
7.27-7.29(1H,m), 7.50-7.57(1H,m), 7.63(1H,s).

MS (FAB) m/z: 655 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 657 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 [Example B-182] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[3-(thien-2-yl)propyl]piperazine  
hydrochloride

In N,N-dimethylformamide (15 ml) were dissolved 1-[(5-  
15 chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[3-(thien-2-yl)propyl]piperazine (257 mg), lithium 6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (129 mg),  
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (131 mg) and 1-hydroxybenzotriazole hydrate (76.4 mg).

20 Under ice cooling, diisopropylethylamine (180 μl) was added dropwise to the resulting solution, followed by stirring at room temperature for 15.5 hours. The reaction mixture was extracted with methylene chloride and water. The organic layer was washed with saturated aqueous NaCl solution,  
25 dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was

subjected to column chromatography (2% methanol - methylene chloride) using as a carrier silica gel. After conversion into the corresponding hydrochloride by the addition of 1N aqueous hydrochloric acid in ethanol, methylene chloride -  
 5 methanol - ether was added to solidify the hydrochloride. The resulting solid was purified again by subjecting it to thin-layer chromatography (10% methanol - methylene chloride), followed by the addition of 1N aqueous hydrochloric acid in ethanol to form the corresponding  
 10 hydrochloride. Methylene chloride - methanol - ether was added to solidify the hydrochloride. The resulting solid was collected by filtration, washed with ether and then dried, whereby the title compound (62.6 mg) was obtained as colorless powder.

15  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.45-2.00 (4H,m), 2.30-3.80 (11H,m), 4.30-4.80 (3H,m), 5.15-5.65 (1H,m), 6.75-6.85 (1H,m), 6.85-6.95 (1H,m), 7.01 (1H,s), 7.20-7.35 (2H,m), 7.48 (1H,d,J=9.0Hz), 7.75 (1H,s), 11.42 (1H,br), 12.44 (1H,s).  
 MS (FAB)  $m/z$ : 604  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 606  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

20 [Example B-183] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[3-(3,4-dimethoxyphenyl)propyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-182, the title  
 25 compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.40-1.90 (4H,m), 2.40-2.70 (1H,m),

2.90 (3H, s), 3.00-3.20 (2H, m), 3.30-3.80 (16H, m), 4.30-  
 4.80 (3H, m), 5.20-5.60 (1H, m), 6.60-6.70 (1H, m),  
 6.82 (1H, d, J=8.1 Hz), 7.01 (1H, s), 7.25-7.35 (1H, m),  
 7.48 (1H, d, J=8.8 Hz), 7.70-7.80 (1H, m), 11.20-11.50 (1H, br),  
 12.43 (1H, s).

MS (FAB) m/z: 658 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 660 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-184] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-[(pyrrolidin-1-yl)sulfonyl]ethyl]piperazine hydrochloride

In the same manner as in Example B-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.80-1.90 (4H, m), 2.10-2.30 (2H, m), 2.40-3.85 (15H, m), 2.90 (3H, s), 4.30-4.90 (3H, m), 5.30-5.50 (1H, m),  
 7.02 (1H, s), 7.25-7.35 (1H, m), 7.48 (1H, d, J=8.8 Hz),  
 7.76 (1H, s), 11.27 (1H, br), 12.44 (1H, s).

MS (FAB) m/z: 641 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 642 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-185] 1-[[6-Methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl]carbonyl]-4-[(1-phenylsulfonyl-5-trimethylsilylethynyl)indol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-103, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.25-0.35 (9H, m), 2.45-2.55 (3H, m), 2.55-2.65 (2H, m), 2.65-2.75 (2H, m), 3.45-3.55 (6H, m), 3.85-3.95 (4H, m), 7.40-7.65 (6H, m), 7.70-7.75 (1H, m), 8.00-

8.05 (2H, m), 8.20-8.25 (1H, m).

MS (FAB) m/z: 665 (M+H)<sup>+</sup>.

[Example B-186] 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-104, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.47 (3H, s), 2.50-2.60 (2H, m), 2.65 (2H, t, J=5.6 Hz), 3.17 (4H, t, J=5.0 Hz), 3.46 (2H, s), 3.90 (4H, br s), 6.84 (1H, s), 7.00 (1H, d, J=1.0 Hz), 7.35-7.40 (1H, m), 7.45-7.50 (1H, m), 7.87 (1H, s), 8.92 (1H, br s).

MS (FAB) m/z: 453 (M+H)<sup>+</sup>.

[Example B-187] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.76 (2H, br), 2.89 (3H, s), 3.05-3.10 (2H, m), 3.35-3.50 (2H, m), 3.74 (4H, br), 4.10-4.60 (2H, m), 6.97 (1H, s), 7.00-7.05 (1H, m), 7.30-7.35 (1H, m), 7.49 (1H, d, J=9.0 Hz), 7.78 (1H, d, J=2.0 Hz), 10.88 (1H, br s), 12.45 (1H, s).

MS (FAB) m/z: 463 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 465 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-188] 1-[(2-tert-Butoxycarbonylisoindolin-5-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.51(9H,s), 3.13(4H,br s), 3.72(4H,br s),  
4.60-4.70(4H,m), 6.96(1H,s), 7.18-7.30(3H,m), 7.31-  
5 7.40(2H,m), 7.69(1H,s), 8.93(1H,s).

MS (FAB) m/z: 545 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 547 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>26</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>5</sub>S·H<sub>2</sub>O

Calculated: C, 55.46; H, 5.55; N, 9.95.

Found: C, 55.69; H, 5.35; N, 9.85.

10 [Example B-189] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-  
[(isoindolin-5-yl)carbonyl]piperazine

In the same manner as in Example B-1, the title compound was obtained.

m.p. 196-199°C (dec).

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.08(4H,br s), 3.44(2H,br s),  
3.69(2H,br s), 4.47(2H,s), 4.50(2H,s), 7.02(1H,s), 7.30-  
7.45(4H,m), 7.51(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz),  
9.65(2H,br s), 12.44(1H,s).

MS (FAB) m/z: 445 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 447 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 Elementary analysis for C<sub>21</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>3</sub>S

Calculated: C, 48.75; H, 5.06; Cl, 13.70; N, 10.83; S,  
6.20.

Found: C, 49.06; H, 4.96; Cl, 13.61; N, 10.63; S,  
6.08.

25 [Example B-190] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(2-

methylisoindolin-5-yl)carbonyl]piperazine

In the same manner as in Example B-32, the title compound was obtained.

m.p. 175-180°C (dec).

5  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.97(3H,br s), 3.09(4H,br s),  
3.43(2H,br s), 3.68(2H,br s), 4.57(4H,br s), 7.02(1H,s),  
7.30-7.45(4H,m), 7.51(1H,d,J=9.0Hz), 7.79(1H,s),  
11.58(1H,br s), 12.46(1H,s).

MS (FAB)  $m/z$ : 459 [(M+H) $^+$ , Cl $^{35}$ ], 461 [(M+H) $^+$ , Cl $^{37}$ ].

10 Elementary analysis for  $\text{C}_{22}\text{H}_{23}\text{ClN}_4\text{O}_3\text{S}\cdot 0.95\text{HCl}\cdot 1.6\text{H}_2\text{O}$   
Calculated: C, 50.58; H, 5.24; Cl, 13.23; N, 10.72; S,  
6.14.

Found: C, 50.90; H, 5.46; Cl, 13.10; N, 10.32; S,  
5.97.

15 [Example B-191] 1-[(5-Chloroindol-2-yl)sulfonyl]-3-[N-(2-  
hydroxyethyl)carbamoylemethyl-4-(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
hydrochloride

20 In the same manner as in Example B-62, the title  
compound was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 2.30-3.82(20H,m), 2.90(3H,s), 4.30-  
4.50(2H,m), 4.50-4.75(1.5H,m), 5.00-5.10(0.5H,m), 5.28-  
5.38(0.5H,m), 5.80-5.90(0.5H,m), 7.02(1H,s),  
7.31(1H,d,J=8.8Hz), 7.48(1H,d,J=8.8Hz), 7.76(1H,s), 7.95-  
25 8.05(1H,m), 11.24(0.5H,m), 11.39(0.5H,m), 12.43(1H,s).



FAB-MS m/z: 580 [(M+H)<sup>+</sup>-H, Cl<sup>35</sup>], 582 [(M+H)<sup>+</sup>-H, Cl<sup>37</sup>].

[Example B-192] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(1,4-dioxo-8-azaspiro[4,5]decan-8-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.79-3.73(22H,m), 2.89(3H,s), 3.93(4H,s), 4.43-4.75(2H,m), 5.55(1H,m), 7.01(1H,d,J=6.1Hz), 7.30(1H,dd,J=1.9,8.8Hz), 7.49(1H,d,J=8.8Hz), 7.76(1H,s), 12.45(1H,s).

MS (FAB) m/z: 649 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 651 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-193] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(1,3-dioxolan-2-yl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.77(2H,m), 2.22(2H,m), 2.49-3.95(15H,m), 4.55-5.03(3H,m), 5.66(1H,m), 6.94(1H,s), 7.28-7.37(2H,m), 7.64(1H,d,J=1.7Hz), 9.34(1H,s).

MS (FAB) m/z: 566 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 568 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-194] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(2-1,3-dioxoisindol-2-yl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title

compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.42-2.45 (3H,m), 2.55-2.84 (5.5H,m), 3.31-3.57 (2H,m), 3.70-3.92 (4.5H,m), 4.42-4.51 (1H,m), 4.61 (2/3H,broad d,J=12.7Hz), 5.25 (1/3H,broad), 5.82 (1/3H,broad), 6.22 (2/3H,broad d,J=9.7Hz), 6.99 (1H,s), 7.30-7.38 (2H,m), 7.62-7.73 (5H,m), 7.79 (2/3H,m), 8.97 (1/3H,broad).

MS (FAB) m/z: 639 (M+H)<sup>+</sup>.

[Example B-195] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-naphthoxy)ethyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.28-2.51 (5H,m), 2.55-2.60 (2H,m), 2.78-2.87 (4H,m), 3.26-3.29 (1H,m), 3.52-3.63 (2H,m), 3.84-3.87 (2H,m), 4.06-4.19 (2H,m), 4.61 (2/3H,broad d,J=12.7Hz), 5.16 (1/3H,broad), 5.71 (1/3H,broad m), 6.22 (2/3H,broad), 6.87-6.94 (2H,m), 7.09 (1H,broad), 7.22-7.33 (3H,m), 7.39-7.43 (1H,m), 7.64-7.74 (4H,m), 9.09 (1H,broad s).

MS (FAB) m/z: 650 (M+H)<sup>+</sup>.

[Example B-196] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-phenoxyethyl)piperazine

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.26-2.40 (2H,m), 2.47 (3H,s), 2.55-2.61 (1H,m), 2.67-2.85 (5H,m), 3.24-3.30 (1/3H,m), 3.48-3.51 (2/3H,m), 3.62-3.65 (2H,m), 3.82-4.08 (4H,m), 4.61 (2/3H,broad d,J=13.9Hz), 5.12 (1/3H,broad), 5.82 (1/3H,broad d,J=12.9Hz), 6.18 (2/3H,broad), 6.68-6.70 (1H,m), 6.87-6.92 (2H,m), 6.95 (1H,s), 7.21-7.23 (2H,m), 7.29-7.35 (2H,m), 7.65 (1H,s), 8.02 (1/3H,s), 9.03 (2/3H,broad s).

MS (FAB) m/z: 599 (M<sup>+</sup>, Cl<sup>35</sup>), 601 (M<sup>+</sup>, Cl<sup>37</sup>).

10 [Example B-197] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-hydroxyethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.88-1.94 (2H,m), 2.48 (3H,s), 2.41-2.62 (2H,m), 2.75-2.90 (4H,m), 3.12-3.21 (1H,m), 3.33-3.85 (6H,m), 4.66 (2/3H,broad d,J=13.7Hz), 4.88-4.90 (1/3H,m), 5.37-5.40 (2/3H,m), 6.18 (1/3H,broad d,J=13.4Hz), 6.91-6.95 (1H,m), 7.29-7.37 (2H,m), 7.65 (1H,s), 9.02 (1H,broad s).

20 MS (FAB) m/z: 524 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 526 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-198] 4-(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

25 In the same manner as in Example B-62, the title

compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.90 (1H, broad), 2.23-2.32 (1H, broad m),  
2.48 (3H, s), 2.65 (2H, broad m), 2.80 (2H, broad s), 2.87-  
2.89 (2H, broad m), 3.21-3.45 (3H, broad m), 3.56 (2H, broad m),  
5 3.67 (2H, s), 3.76-4.04 (2H, broad m), 4.29-4.41 (2H, m),  
4.62 (2/5H, broad d, J=10.4Hz), 4.75 (3/5H, broad),  
4.62 (3/5H, broad d, J=14.6Hz), 5.90 (2/5H, broad), 6.97 (1H, s),  
7.29 (1H, dd, J=1.9, 8.7Hz), 7.41 (1H, broad m), 7.63 (1H, s).

MS (FAB) m/z: 593 (M+H)<sup>+</sup>.

10 [Example B-199] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazin-2-yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-82, the title compound was obtained.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.65 (3H, br s), 2.76 (3H, br s),  
3.13 (4H, br s), 3.74 (2H, br s), 4.10-4.50 (6H, br),  
7.03 (1H, d, J=1.5Hz), 7.31 (1H, dd, J=8.8, 2.0Hz),  
7.48 (1H, d, J=8.8Hz), 7.76 (1H, d, J=2.0Hz), 12.42 (1H, br s).  
MS (FAB) m/z: 495 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 497 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example B-200] 2-[[[4-tert-Butoxycarbonylpiperazin-1-yl)carbonyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-79, the title  
25 compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49 (9H, s), 2.49 (3H, s), 2.55-3.20 (8H, m),  
 3.30-3.85 (12H, m), 3.95-4.04 (0.5H, m), 4.10-4.18 (0.5H, m),  
 4.55-4.67 (0.5H, m), 4.95-5.07 (0.5H, m), 5.55-5.65 (0.5H, m),  
 6.00-6.10 (0.5H, m), 7.00 (1H, s), 7.25-7.31 (1H, m),  
 5 7.37 (1H, d,  $J=8.8\text{Hz}$ ), 7.65 (1H, s).

MS (FAB)  $m/z$ : 706  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 708  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example B-201] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(piperazin-1-yl)carbonyl]methyl]piperazine  
 10 hydrochloride

In the same manner as in Example B-1, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.50-3.85 (23H, m), 4.30-4.45 (1H, m),  
 4.60-4.75 (0.5H, m), 5.00-5.10 (0.5H, m), 5.30-5.40 (0.5H, m),  
 15 5.80-5.95 (0.5H, m), 7.03 (1H, s), 7.32 (1H, d,  $J=8.8\text{Hz}$ ),  
 7.50 (1H, d,  $J=8.8\text{Hz}$ ), 7.78 (1H, s), 9.20-9.45 (1H, br),  
 12.46 (1H, br s).

MS (FAB)  $m/z$ : 606  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 608  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Example B-202] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-furfurylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 20 hydrochloride

In the same manner as in Example B-79, the title compound was obtained.

25  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.50-3.50 (13H, m), 3.60-3.85 (2H, m),

4.12-4.50 (3H,m), 4.60-4.75 (0.5H,m), 5.05-5.10 (0.5H,m),  
 5.30-5.40 (0.5H,m), 5.78-5.90 (0.5H,m), 6.17-6.25 (1H,br),  
 6.35-6.42 (1H,m), 7.03 (1H,s), 7.31 (1H,d,J=8.8Hz),  
 7.48 (1H,d,J=8.8Hz), 7.51-7.58 (1H,m), 7.77 (1H,s), 8.41-  
 5 8.55 (1H,br), 12.44 (1H,br s).

MS (FAB) m/z: 617 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 619 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

HRMS (FAB) m/z: 617.1418 (M+H)<sup>+</sup> (calcd for C<sub>27</sub>H<sub>29</sub>ClN<sub>6</sub>O<sub>5</sub>S<sub>2</sub>,  
 617.1408).

[Example B-203] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-  
 10 methoxy-N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 hydrochloride

In the same manner as in Example B-79, the title  
 compound was obtained.

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.50-3.83 (20H,m), 4.30-4.80 (2.5H,br),  
 5.07 (0.5H,br s), 5.31-5.36 (0.5H,br), 5.78 (0.5H,br s),  
 7.03 (1H,s), 7.31 (1H,d,J=9.2Hz), 7.48 (1H,d,J=9.2Hz),  
 7.77 (1H,s), 11.04 (1H,br s), 12.45 (1H,br s).

MS (FAB) m/z: 581 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 583 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example B-204] 1-[(6-(tert-Butoxycarbonyl)-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-  
 chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Example B-62, the title  
 compound was obtained.

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48 (9H,s), 2.85 (2H,br s), 3.22 (4H,br s),

3.73(2H,br s), 3.89(2H,br s), 4.58(2H,br s), 4.65(2H,br s),  
6.97(1H,s), 7.32(1H,dd,J=8.8,2.0Hz), 7.37(1H,d,J=8.8Hz),  
7.66(1H,d,J=2.0Hz), 8.72(1H,s).

MS (FAB) m/z: 566 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 568 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Example B-205] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-  
[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-1, the title  
compound was obtained.

10 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.01(2H,t,J=6.1Hz), 3.13(4H,br s),  
3.44(2H,t,J=6.1Hz), 3.75(2H,br s), 4.36(2H,br s),  
4.42(2H,s), 7.04(1H,s), 7.31(1H,dd,J=8.8,2.0Hz),  
7.49(1H,d,J=8.8Hz), 7.77(1H,d,J=2.0Hz), 9.46(2H,br s),  
12.43(1H,s).

15 MS (FAB) m/z: 466 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 468 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-206] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-  
hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

20 In the same manner as in Example B-144, the title  
compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.70-3.05(2H,br), 3.05-3.25(6H,br),  
3.65-4.50(6H,br), 7.03(1H,s), 7.30(1H,dd,J=8.8,2.0Hz),  
7.47(1H,d,J=8.8Hz), 7.76(1H,d,J=2.0Hz), 8.35(1H,s),  
12.40(1H,s).

25 MS (FAB) m/z: 482 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 484 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-207] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-  
[(ethoxycarbonyl)methyl]-1-[(6-methylsulfonyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In a saturated solution of hydrochloride in ethanol  
5 was dissolved 1-(tert-butoxycarbonyl)-4-[(5-chloroindol-2-  
yl)sulfonyl]-2-[(methoxycarbonyl)methyl]piperazine (1.15  
g), followed by stirring at room temperature for 1 hour.  
The solvent was distilled off under reduced pressure.  
Methylene chloride and a saturated aqueous solution of  
10 sodium bicarbonate were added to the residue to separate  
into layers. The organic layer was dried over anhydrous  
sodium sulfate and distilled under reduced pressure to  
remove the solvent. A portion (519 mg) of the residue  
(0.97 g) was dissolved in N,N-dimethylformamide (2 ml),  
15 followed by the addition of lithium (6-tert-butoxycarbonyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carboxylate  
(328 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide  
hydrochloride (288 mg) and 1-hydroxybenzotriazole (363 mg).  
The resulting mixture was stirred at room temperature for 3  
20 days. Methylene chloride and water were added and the  
organic layer was collected. The organic layer was dried  
over anhydrous sodium sulfate and distilled under reduced  
pressure to remove the solvent. The residue was purified  
by flash column chromatography (hexane : ethyl acetate =  
25 1:1) using as a carrier silica gel.

The resulting purified product was dissolved in a



saturated solution (5 ml) of hydrochloride in ethanol, followed by stirring at room temperature for 1 hour. After the addition of methylene chloride, the resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (5 ml), followed by the addition of methanesulfonyl chloride (105  $\mu$ l) and triethylamine (0.5 ml). The resulting mixture was stirred at room temperature for 15 minutes and washed with water. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by flash column chromatography (methylene chloride : methanol = 49:1) using as a carrier silica gel, whereby the title compound (207 mg) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.07-1.16(3H,m), 2.67-2.90(5H,m), 2.96(3H,s), 3.20-3.24(2H,m), 3.53-3.78(4H,m), 3.95-4.04(2H,m), 4.39, 5.04(1H,each d, $J=14.4,14.9\text{Hz}$ ), 4.55(2H,s), 5.03, 5.95(1H,each br s), 7.03(1H,s), 7.31(1H,dd, $J=8.8,1.7\text{Hz}$ ), 7.47(1H,d, $J=8.8\text{Hz}$ ), 7.76(1H,d, $J=1.7\text{Hz}$ ), 12.41(1H,s).

MS (FAB)  $m/z$ : 630 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-208] 2-[Carboxymethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-77, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.32-3.74 (14H, m), 4.38, 5.37 (1H, each  
 5 d, J=12.2, 12.4 Hz), 4.54 (2H, s), 5.00, 5.83 (1H, each br s),  
 7.02 (1H, s), 7.30 (1H, d, J=8.8 Hz), 7.47 (1H, d, J=8.8 Hz),  
 7.75 (1H, s), 12.51 (1H, s).

HRMS (FAB) m/z: 602.0612 (M+H)<sup>+</sup> (calcd for C<sub>22</sub>H<sub>25</sub>N<sub>5</sub>O<sub>7</sub>ClS<sub>3</sub>,  
 602.0605).

10 [Example B-209] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-methylsulfonyl]carbamoyl]methyl]-1-[(6-methylsulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

In tetrahydrofuran (5 ml) was dissolved 2-  
 15 [carboxymethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine (115 mg), followed by the addition of carbonyldiimidazole (58 mg). The resulting mixture was heated under reflux for 2 hours. After cooling to room  
 20 temperature, methanesulfonamide (34 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (55 mg) were added, followed by stirring for 1.5 hours. The solvent was distilled off under reduced pressure. The residue was dissolved in methylene chloride and the solution was washed with water,  
 25 0.2N hydrochloric acid and saturated aqueous NaCl solution. The organic layer was dried over anhydrous sodium sulfate

and distilled under reduced pressure to remove the solvent. The residue was purified by preparative TLC (methylene chloride : methanol = 9:1). The solvent was distilled off under reduced pressure. The solid thus obtained was washed with ether, whereby the title compound (62 mg) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.50-3.56 (15H, m), 3.65-3.77 (2H, m), 4.40, 5.40 (1H, each d,  $J=15.4, 11.8\text{Hz}$ ), 4.55 (2H, s), 5.10, 5.98 (1H, each br s), 7.04 (1H, s), 7.31 (1H, d,  $J=8.8, 2.0\text{Hz}$ ), 7.47 (1H, d,  $J=8.8\text{Hz}$ ), 7.76 (1H, d,  $J=2.0\text{Hz}$ ), 11.88 (1H, s), 12.44 (1H, s).

MS (FAB)  $m/z$ : 602 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-210] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

To a solution of lithium 6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (1.89 g) in  $N,N$ -dimethylformamide (40 ml) were added 1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine (2.50 g), 1-hydroxybenzotriazole monohydrate (1.20 g) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.70 g) at room temperature. After stirring for 2 days, ethyl acetate (200 ml) and water (1.0 l) were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (2 x 150 ml). The organic layers were combined, washed with water (1.0 l) and

a saturated aqueous solution (200 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 200 g, methylene chloride : ethyl acetate = 7:1 → 1:1), whereby 1-[[6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine was obtained as pale yellow foam. A solution of the boc form in methylene chloride (15 ml) was added trifluoroacetic acid (15 ml) at room temperature. After stirring for 10 minutes, the solvent was distilled off under reduced pressure. Methylene chloride (50 ml) and a saturated aqueous solution (150 ml) of sodium bicarbonate were added to the residue to separate it into layers. The water layer was extracted with methylene chloride (6 x 25 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (silica gel: 100 g, methylene chloride : methanol = 25:1 → 10:1), whereby the title compound (754 mg) was obtained as a pale brown solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.67(2H,t,J=5.7Hz), 2.96(2H,t,J=5.7Hz), 3.18(4H,t,J=4.9Hz), 3.31(1H,s), 3.77(2H,br s), 3.90(2H,s), 4.44(2H,br s), 7.57(1H,dd,J=8.8,2.0Hz), 8.05(1H,d,J=8.8Hz),

8.09 (1H, s), 8.31 (1H, d, J=2.0 Hz).

MS (FAB) m/z: 483 (M+H)<sup>+</sup>.

[Example B-211] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-  
4-[[6-(pyridin-4-yl)-4,5,6,7-tetrahydrothiazolo[5,4-  
5 c]pyridin-2-yl]carbonyl]piperazine hydrochloride

To a solution of 1-[(6-chlorobenzo[b]thien-2-  
yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-  
2-yl]carbonyl]piperazine (200 mg) in N,N-dimethylformamide  
(2.0 ml) were added 4-bromopyridine (87.0 mg) and

10 triethylamine (150  $\mu$ l) at room temperature. The resulting  
mixture was stirred under heat at 120°C for 12 hours.

After concentration of the reaction mixture, methylene  
chloride (20 ml), a saturated aqueous solution (50 ml) of  
sodium bicarbonate and water (50 ml) were added to the  
15 concentrate to separate it into layers. The water layer  
thus obtained was extracted with methylene chloride (4 x 20  
ml). The organic layers were combined, dried over  
anhydrous sodium sulfate and distilled under reduced  
pressure to remove the solvent. The residue was purified

20 by preparative thin-layer chromatography (methylene  
chloride : methanol = 20:1) using silica gel, followed by  
purification by preparative thin-layer chromatography  
(methylene chloride : acetone : methanol = 15:5:1) using  
silica gel. The purified product was dissolved in

25 methylene chloride, methanol and 1N hydrochloric acid. The  
resulting solution was concentrated under reduced pressure

and dried, whereby the title compound (56.5 mg) was obtained as a pale yellow solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.97(2H,t,J=5.6Hz), 3.17(4H,br s),  
3.77(2H,br s), 4.05(2H,t,J=5.6Hz), 4.41(2H,br s),  
5.01(2H,s), 7.31(2H,br s), 7.56(1H,d,J=8.4Hz),  
8.05(1H,d,J=8.4Hz), 8.08(1H,s), 8.30(2H,s), 8.32(1H,s),  
13.70(1H,br s).

MS (FAB) m/z: 560 (M+H)<sup>+</sup>.

[Example B-212] 2-(Methoxycarbonylmethyl)-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-  
[[5-(trimethylsilyl)ethynyl]indol-2-yl]sulfonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.26(9H,s), 2.49(3H,s), 2.53-2.68(1H,m),  
2.74(1H,dd,J=12.0,2.7Hz), 2.77-2.83(3H,m), 2.87(2H,br s),  
3.00(1H,dd,J=15.8,8.7Hz), 3.11-3.26(1/2H,br), 3.39-  
3.54(1/2H,br), 3.59-3.67(5H,m), 3.72-3.96(2H,m),  
4.61(1/2H,br d,J=13.2Hz), 5.22(1/2H,br s), 5.71(1/2H,br  
d,J=13.2Hz), 6.16(1/2H,br s), 6.97(1H,s),  
7.34(1H,d,J=8.6Hz), 7.43(1H,dd,J=8.6,1.5Hz), 7.81(1H,s),  
9.35(1H,br d,J=11.0Hz).

MS (FAB) m/z: 614 (M+H)<sup>+</sup>.

[Example B-213] 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-  
(methoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Example B-104, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.49(3H,s), 2.53-2.95(7H,m), 2.95-3.05(1H,m), 3.04(1H,s), 3.20(1/2H,br t, $J$ =11.6Hz),  
 5 3.46(1/2H,br t, $J$ =11.6Hz), 3.59-3.75(5H,m), 3.75-3.97(2H,m),  
 4.62(1/2H,br d, $J$ =12.8Hz), 5.22(1/2H,br s), 5.73(1/2H,br d, $J$ =13.6Hz), 6.18(1/2H,br s), 7.00(1H,s),  
 7.37(1H,d, $J$ =8.6Hz), 7.45(1H,dd, $J$ =8.6,1.2Hz), 7.85(1H,s),  
 9.28(1H,br d, $J$ =13.2Hz).

10 MS (FAB)  $m/z$ : 542 ( $\text{M}+\text{H}$ ) $^+$ .

[Example B-214] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(morpholin-4-yl)sulfonyl]ethyl]piperazine hydrochloride

15 In the same manner as in Example B-182, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.10-2.40(2H,m), 2.50-2.80(2H,m),  
 2.90(3H,s), 3.00-3.30(8H,m), 3.30-3.90(9H,s), 4.30-4.90(3H,m), 5.30-5.50(1H,m), 7.03(1H,s),  
 20 7.31(1H,dd, $J$ =8.8,1.5Hz), 7.48(1H,d, $J$ =8.8Hz),  
 7.76(1H,d, $J$ =1.5Hz), 11.42(1H,br), 12.45(1H,s).

MS (FAB)  $m/z$ : 657 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 659 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Example B-215] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-ethoxycarbonyl)ethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

25

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.15-1.25(3H,m), 1.40-1.80(1H,m), 2.05-2.15(1H,m), 2.25-2.45(3H,m), 2.49(3H,s), 2.50-3.55(6H,m),  
 3.67(2H,s), 3.70-3.90(2H,m), 4.00-4.20(2H,m), 4.55-6.10(2H,m), 6.95(1H,s), 7.30-7.40(2H,m),  
 7.65(1H,d,J=1.6Hz), 9.03(1H,br).

MS (FAB) m/z: 580 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 582 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-216] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[2-(morpholin-4-yl)carbonyl]ethyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.85-2.00(1H,m), 2.05-2.20(1H,m), 2.20-2.35(2H,m), 2.55-2.70(1H,m), 3.80-2.95(4H,m), 3.00-3.80(14H,m), 4.25-5.55(5H,m), 7.02(1H,s),  
 7.30(1H,dd,J=8.8,2.0Hz), 7.48(1H,d,J=8.8Hz),  
 7.75(1H,d,J=2.0Hz), 11.45(1H,br s), 12.43(1H,s).

MS (FAB) m/z: 621 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 623 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-217] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[2-(N,N-dimethylaminocarbonyl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 319, the title compound was obtained.



<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.85-2.00 (1H,m), 2.05-2.20 (1H,m), 2.20-2.35 (2H,m), 2.50-2.65 (1H,m), 2.70-3.80 (17H,m), 4.30-5.55 (4H,m), 7.02 (1H,s), 7.29 (1H,dd,J=8.8,2.0Hz), 7.48 (1H,d,J=8.8Hz), 7.75 (1H,d,J=2.0Hz), 11.49 (1H,br s),  
 5 12.44 (1H,s).

MS (FAB) m/z: 579 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 581 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-218] 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine hydrochloride

10 In the same manner as in Example B-182, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.90-2.18 (2H,m), 2.20-2.90 (4H,m), 2.90 (3H,s), 3.12 (2H,br s), 3.21-3.82 (6H,m), 4.30-4.85 (2H,m), 5.31-5.43 (0.5H,m), 5.55-5.70 (0.5H,m),  
 15 7.02 (1H,d,J=2.0Hz), 7.31 (1H,dd,J=8.9,2.1Hz), 7.48 (1H,d,J=8.8Hz), 7.76 (1H,d,J=1.7Hz), 11.18 (1H,br s), 12.44 (1H,br s).

MS (FAB) m/z: 533 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 535 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Example B-219] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.93 (2H,t,J=6.6Hz), 2.73-3.32 (10H,m),  
 25 3.73 (1H,br s), 3.93 (4H,s), 3.95 (1H,br s), 6.97, 7.03 (1H,s),

7.30 (1H, dd, J=8.8, 2.2 Hz), 7.45-7.47 (1H, m), 7.76 (1H, s).

MS (FAB) m/z: 523 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 525 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-220] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-oxo-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)carbonyl]piperazine

In a 300-mL egg-plant type flask was charged 1-[(5-chloroindol-2-yl)sulfonyl]-4-[(6,6-ethylenedioxy-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)carbonyl]piperazine (740 mg), followed by dissolution in methanol (150 mL). To the resulting solution was added p-toluenesulfonic monohydrate (100 mg), followed by heating under reflux. After 16 hours, the reaction was terminated and the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (silica gel: 75 g, ethyl acetate : hexane = 1:1), whereby the title compound (110 mg) was obtained as a pale yellow amorphous solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.76 (2H, t, J=6.8 Hz), 3.18 (2H, t, J=6.8 Hz), 3.19-3.22 (6H, m), 3.65 (2H, s), 3.89 (1H, br s), 4.59 (1H, br s), 6.97 (1H, s), 7.31-7.39 (2H, m), 7.66 (1H, d, J=2.0 Hz).

MS (FAB) m/z: 479 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 481 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-221] 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4,5-dihydro-7H-pyrano[4,3-d]thiazol-2-yl)carbonyl]piperazine

In the same manner as in Example B-62, the title compound was obtained.

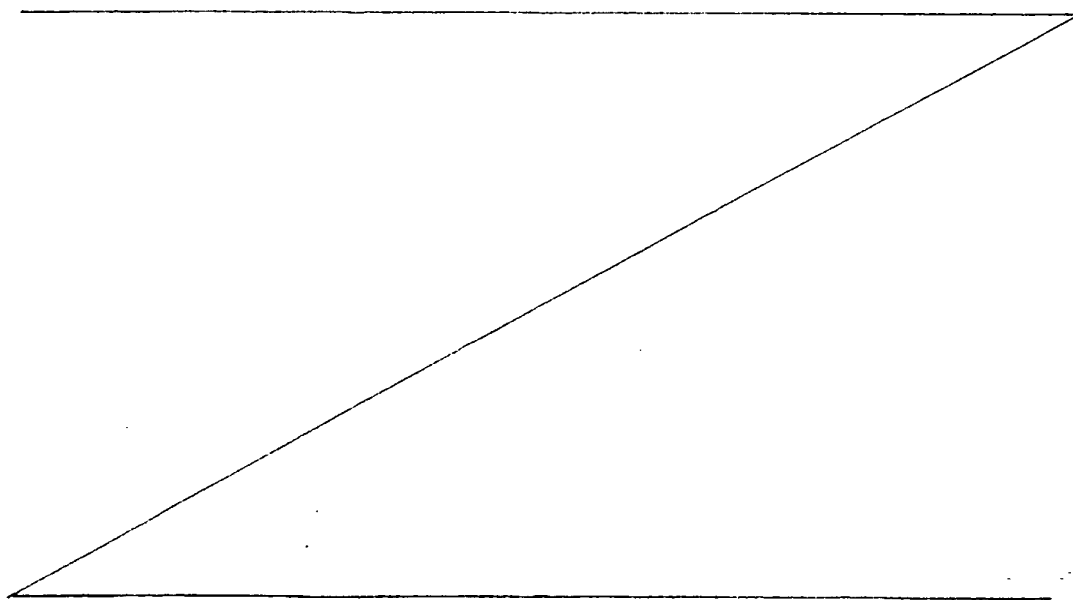
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.82 (2H, t, J=5.6 Hz), 3.12 (4H, t, J=4.9 Hz),

3.28-3.35 (2H, m), 3.73 (1H, br s), 3.93 (2H, t,  $J=5.6\text{Hz}$ ),  
4.39 (1H, br s), 4.79 (2H, s), 7.03 (1H, s),  
7.30 (1H, dd,  $J=8.8, 2.2\text{Hz}$ ), 7.47 (1H, d,  $J=8.8\text{Hz}$ ), 7.76 (1H, s).  
MS (FAB)  $m/z$ : 467  $[(M+H)^+, Cl^{35}]$ , 469  $[(M+H)^+, Cl^{37}]$ .

- 5 [Example B-222] 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[N-(phenylsulfonyl)carbamoyl]methyl]piperazine hydrochloride

10 In the same manner as in Example B-62, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ : 2.52-3.77 (12H, m), 3.88-4.20 (2H, m),  
4.24-4.48 (1.5H, m), 4.52-4.75 (1H, m), 5.00 (0.5H, m), 5.23-  
5.32 (0.5H, m), 5.57 (0.25H, br s), 5.79 (0.25H, br s),  
6.97 (1H, s), 7.28 (1H, d,  $J=8.8\text{Hz}$ ), 7.45 (1H, d,  $J=8.8\text{Hz}$ ), 7.49-



7.53(1H,m), 7.61(2H,br s), 7.72(1H,s), 7.85(2H,br s),  
11.54-11.98(1H,m), 12.20-12.50(2H,m).

MS (FAB) m/z: 677 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 679 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-223] 1-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-  
5 methyl-N-methylsulfonylcarbamoyl)methyl]-4-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine hydrochloride

In the same manner as in Example B-62, the title  
compound was obtained.

10 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.12-4.53(21H,m), 3.75-3.82(0.5H,m),  
4.35-4.45(1H,m), 5.09(0.5H,br s), 5.32-5.49(0.5H,m),  
5.85(0.5H,br s), 7.02(1H,s), 7.30(1H,dd,J=8.8,2.0Hz),  
7.47(1H,dd,J=8.8,2.0Hz), 7.75(1H,s), 12.44(1H,br s).

MS (FAB) m/z: 629 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 631 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

15 [Example B-224] 4-(5-Chloroindol-2-yl)sulfonyl]-2-[(2-  
methylsulfonylhyrazino)carbonylmethyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine hydrochloride

20 In the same manner as in Example B-62, the title  
compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.10-4.60(17H,m), 5.10-5.25(1.5H,m),  
5.40-5.55(1H,m), 5.90(0.5H,br s), 6.11-6.20(0.5H,m),  
6.74(0.5H,br s), 7.81(1H,s), 8.10(1H,d,J=8.6Hz),  
8.27(1H,d,J=8.6Hz), 8.56(1H,s), 10.15-10.25(1H,m),  
25 11.08(1H,s), 11.99(1H,s), 13.22(1H,s).

MS (FAB) m/z: 630 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 632 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Example B-225] 1-[[5(6)-chlorobenzimidazol-2-yl-  
]sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl)carbonyl]piperazine

5           1-[[5(6)-chlorobenzimidazol-2-yl-]sulfonyl]pyperazine  
(225 mg), 1-hydroxybenztriazole (11 mg) and 1-ethyl-3-(3-  
dimethylaminopropyl)-carbodiimide (148 mg) were  
successively added to a N,N-dimethylformamide solution  
(3.0 ml) containing lithium 6-methyl-4,5,6,7-  
10 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carboxylate (153 mg),  
and stirred at room temperature for 28 hours. After  
concentration under reduced pressure, the reaction solution  
was divided into two layers by adding a dichloromethane and  
saturated sodium chloride solution. The organic layer was  
15 washed with a saturated sodium chloride solution, dried  
over sodium sulfate, and concentrated under reduced  
pressure. The obtained product was purified by  
chromatography on a silica gel column  
(dichloromethane:methanol = 20:1), concentrated by adding  
20 ethanol (2 ml) and a 1N aqueous hydrochloride in ethanol  
(1.5 ml), and dried. Thus, the title compound (168 mg) was  
obtained as colorless amorphous.

IR (KBr) cm<sup>-1</sup> 1622, 1429, 1365, 1279, 1157, 1055, 1005, 970,  
939, 922.

25   <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ, 2.90 (3H, s), 3.03-4.00 (10H, br), 4.40  
(3H, br s), 4.63-4.77 (1H, m), 7.40 (1H, dd, J = 8.8, 2.0

Hz), 7.72 (1H, d, J = 8.8 Hz), 7.78 (1H, s), 11.48-11.65 (1H, br s).

MS (FAB) m/z 481 [(M + H)<sup>+</sup>, Cl<sup>35</sup>], 483 [(M + H)<sup>+</sup>, Cl<sup>37</sup>].

[Test 1] Measurement of FXa inhibitory action (IC<sub>50</sub>)

5           In a 96-well microtiter plate, 10 µl of a sample solution, 40 µl of a 100 mM tris · 200mM sodium chloride · 0.2% BSA (pH: 7.4) buffer and 10 µl of 0.05 U/ml human FXa ("Cosmobio-ERL HFXa-1011", dissolved in and diluted with a measuring buffer) were poured in portions, followed by the  
10       addition of 40 ml of 750 µM S2222 (product of Chromogenix). An increase (mOD/min) in the absorbance at 405 nm was measured at room temperature. From the below-described equation, an inhibitory ratio % of each sample was determined. On a logarithmic probability paper, the final  
15       concentration of the sample and inhibitory ratio % were plotted along the abscissa and the ordinate, respectively, whereby a 50% inhibitory concentration (IC<sub>50</sub>) was determined.

          Inhibitory ratio (%) = (1 - OD of sample ÷ OD of  
20       control) x 100  
      (Results)

          The compound of the formula (I) having, in the structure thereof, an unsubstituted pyridylphenyl group as the group Q<sup>1</sup>-Q<sup>2</sup>- and a 7-chloronaphthyl, 5-  
25       chlorobenzofuranyl, 6-chlorobenzofuranyl, 5-chlorobenzothienyl or 5-chloro-1-methylindole group as the

group Q<sup>A</sup> is found to have FXa activity 50% inhibitory concentration (IC<sub>50</sub>) of 100 nM or greater (refer to Table 1).

Table 1

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-1	123
Compound of Example A-17	180
Compound of Example A-83	2800
Compound of Example A-85	1000
Compound of Example A-86	>10000
Compound of Example A-91	7000
Compound of Example A-96	450
Compound of Example A-106	420

5

The compound similar to the compound of Example A-1 except for having a substituted pyridylphenyl group, pyridylpyrimidinyl group, pyridylpyrazyl group or pyridylpyridyl group instead of the pyridylphenyl group is found to have FXa inhibitory action improved by several times as much as that of the compound of Example A-1 (refer to Table 2).

10

Table 2

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-152	38
Compound of Example A-155	28
Compound of Example A-123	23
Compound of Example A-137	60
Compound of Example A-4	54

The compound similar to that of Example A-1 except for having, as the group Q<sup>A</sup>, a 6-chlorobenzothienyl group, 5-ethynylindolyl group or 5-chloroindolyl group instead of chloronaphthyl group is found to be particularly excellent in FXa inhibitory action (refer to Table 3).

Table 3

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-90	16
Compound of Example A-101	9.5
Compound of Example A-103	27
Compound of Example A-181	15
Compound of Example A-97	82
Compound of Example A-98	125

The compound having, as the group Q<sup>1</sup>-Q<sup>2</sup>-, a



pyridylphenyl group is found to show a drastic improvement in the FXa inhibitory action when the nitrogen atom on the pyridine ring has been converted into N-oxide and the group Q<sup>A</sup> represents a 6-chlorobenzothienyl group, 5-ethynylindolyl group or 5-chloroindolyl group (refer to Table 4).

Table 4

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-107	4.7
Compound of Example A-117	10.5
Compound of Example A-109	6.9
Compound of Example A-116	8.6
Compound of Example A-181	2.9
Compound of Example A-120	14

The compound having, as the group Q<sup>1</sup>-Q<sup>2</sup>-, a heteroaryl group such as pyridylpyrimidinyl, pyridylpyrazinyl or pyridylthiazolyl group and, as the group Q<sup>A</sup>, a 6-chlorobenzothienyl, 6-ethynylbenzothienyl, 5-chloroindolyl or 5-ethynylindolyl group is found to be improved in FXa inhibitory action (refer to Table 5).

Table 5

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-132	5.6
Compound of Example A-133	10
Compound of Example A-105	2.4
Compound of Example A-134	4.6
Compound of Example A-138	5
Compound of Example A-140	6.8
Compound of Example A-131	19
Compound of Example A-135	14
Compound of Example A-183	4.7
Compound of Example A-185	6.3
Compound of Example A-186	1.9
Compound of Example A-229	1.6
Compound of Example A-231	2.3
Compound of Example A-239	3.5
Compound of Example A-216	15
Compound of Example A-296	1.3

The compound having one or two substituents introduced in the group Q<sup>3</sup> is found to exhibit strong FXa inhibitory activity (refer to Table 6).

Table 6

Sample compound	Concentration (nM) of the sample at which 50% of Fxa activity is inhibited
Compound of Example A-130	3.6
Compound of Example A-173	10
Compound of Example A-105	20
Compound of Example A-224	7.6
Compound of Example A-259	3.5
Compound of Example A-277	2.7
Compound of Example A-279	10
Compound of Example A-293	1.9
Compound of Example A-298	0.7

Compounds of Examples B-32, B-54, B-61, B-63 and B-99 exhibited FXa 50% inhibitory concentrations of 20 nM, 5.0 nM, 30 nM, 12.5 nM and 1.7nM, respectively.

[Test 2] Measurement of thrombin inhibitory action (IC<sub>50</sub>)

In a 96-well microtiter plate, 10  $\mu$ l of a sample solution, 40  $\mu$ l of a 100 mM tris · 200mM sodium chloride · 0.2% BSA (pH: 7.4) buffer and 10  $\mu$ l of 4 U/ml human thrombin (Sigma Chemical, dissolved in and diluted with a measuring buffer) were poured in portions, followed by the addition of 40  $\mu$ l of 500  $\mu$ M S2266 (product of Chromogenix). An increase (mOD/min) in the absorbance at 405 nm was measured at room temperature. From the below-described equation, an inhibitory ratio % of each sample was

determined. On a logarithmic probability paper, the final concentration of the sample and inhibitory ratio % were plotted along the abscissa and the ordinate, respectively, whereby a 50% inhibitory concentration (IC<sub>50</sub>) was found.

5            Inhibitory ratio (%) = (1 - OD of sample ÷ OD of control) x 100

          The compound having, in the structure thereof, a heteroaryl group such as pyridylpyrimidinyl or pyridylpyrazinyl, a 6-chlorobenzothienyl group, a 6-ethynylbenzothienyl, a 5-ethynylindolyl group or a 5-chloroindolyl group; or the compound having, in the structure thereof, a 6-chlorobenzothienyl, 6-ethynylbenzothienyl, 5-ethynylindolyl or 5-chloroindolyl group, in addition to a heteroaryl group such as  
10            pyridylpyrimidinyl or pyridylpyrazinyl is found to exhibit  
15            markedly low thrombin-activity inhibitory action compared with excellent FXa inhibitory action (refer to Tables 7 and 8).

Table 7

Sample compound	Concentration (nM) of the sample at which 50% of thrombin activity is inhibited
Compound of Example A-117	4100
Compound of Example A-137	4100
Compound of Example A-123	16000
Compound of Example A-109	1550
Compound of Example A-132	> 100000
Compound of Example A-133	7700
Compound of Example A-216	>50000

Table 8

Sample compound	Concentration (nM) of the sample at which 50% of thrombin action is inhibited
Compound of Example A-105	19000
Compound of Example A-134	10200
Compound of Example A-138	5900
Compound of Example A-140	1370
Compound of Example A-103	2220

5           The compound of Example B-54 exhibited a thrombin 50% inhibitory concentration of 1.05  $\mu$ M.

[Test 3] Measurement of coagulation extending action  
(measurement of prothrombin time)

10           Plasma (20  $\mu$ l) and 20  $\mu$ l of a sample solution were mixed. To the resulting mixture, 40 ml of cynplastin

(product of Organon Teknika) was added and the coagulation time was measured. The concentration of the sample (CT2) at which the coagulation time of the plasma was increased twice was found and it was designated as an index of anticoagulant action.

The compound of Example 33 showed CT2 of 0.35  $\mu$ M.

#### [Test 4] Test of oral administration

##### 1) Method

A sample was dissolved or suspended in a 0.5% (w/v) methyl cellulose solution and the resulting solution or suspension was orally administered (10 ml/kg) to a 8 to 11 week-old rat (Wistar male rat (Nippon SLC Co., Ltd.)) which had been fasted overnight. After administration of the sample, the blood to which 1/10 part by weight of 3.13% (w/v) sodium citrate had been added was collected from the cervical vein under anesthesia with halothane. The rat was awakened except during the blood collection. Feeding was re-started 6 hours after the blood collection. From each blood sample, the plasma was separated by centrifugal separation and anti-FXa activity in the blood and prothrombin time extending action were measured.

##### 2) Measuring method

###### 2-1) Measurement of anti-FXa activity in the plasma

In a 96-well plate, 5  $\mu$ l of the plasma was poured in portions, followed by the addition of 55  $\mu$ l of a 8:1:2 mixture of 100 mM tris · 200 mM sodium chloride · 0.2% BSA

(pH 7.4) buffer, water and 0.1 U/ml human Factor Xa solution (dissolved in and diluted with a measuring buffer) and 40  $\mu$ l of 750  $\mu$ M S-2222. After stirring for 10 seconds in a plate mixer, an increase (mOD/min) of the absorbance at 405 nm was measured at room temperature. The inhibitory ratio was calculated as follows:

An inhibitory ratio (%) =  $(1 - \text{OD of sample} \div \text{OD of control on average relative to blood-collecting time of sample}) \times 100$

2-2) Measurement of coagulation extending action in oral administration (measurement of prothrombin time)

To 20  $\mu$ l of the plasma, 40  $\mu$ l of cynplastin (Organon Teknika/USA) was added and the coagulation time was measured. The ratio of the prothrombin time after the administration of the sample relative to the prothrombin time before the administration of the sample was designated as an index of the coagulation extending action.

### 3) Results

The compound of Example A-60 showed an anti-FXa activity of 70% in the plasma one hour after the oral administration of 30 mg/kg of the sample. It extended the prothrombin time by 1.18 times.

The compound of Example B-36 showed an anti-FXa activity of 68% in the plasma one hour after the oral administration of 30 mg/kg of the sample. It extended the thrombin time.

[Test 5] Testing method of anti-thrombus effects in a tissue thromboplastin-derived rat DIC model

A rat was anesthetized with halothane. After the collection of the blood (for measurement of the number of platelets, anti-FXa activity and TAT) from its cervical vein by using 1/10 part by weight of 3.13% (w/v) sodium citrate, the sample was administered orally. At an appropriate time after the administration, the rat was intraperitoneally anesthetized (1 mg/kg) with Nembutal (50 mg/ml pentobarbital sodium, Abott Laboratories), followed by intravenous drip of 0.2 U/ml of tissue thromboplastin (Thromboplastin C plus, Dade Diagnostics of P. R. Inc.,) from the femoral vein for one minute at a rate of 2.5 to 3.0 ml/kg/min. The blood was collected (for measuring the number of platelets and anti-FXa activity) from the cervical vein 10 minutes after the intravenous drip and the blood was collected (for measuring TAT) from the cervical vein 20 minutes after the blood collection. The number of platelets, anti-FXa activity in the plasma and TAT concentration of each blood sample were measured. The number of the platelets was measured by an automatic cytometer, while the anti-FXa activity in the plasma was measured in a similar manner to that described in Test 4.

For the measurement of TAT (Thrombin-anti Thrombin = complex), EnzygnostR TAT micro kit (Boering Verke) was employed.



As a result of the oral administration of 30 mg/kg of the compound of Example B-36, apparent anti-FXa action in the plasma was recognized and a decrease in the number of the platelets and an increase in the TAT concentration were suppressed (the tissue thromboplastin was administered one hour after the administration of the sample).

### **Capability of Exploitation in Industry**

The compound according to the present invention has peculiar and excellent FXa inhibitory action so that it is useful as a coagulation suppressor, or a preventive and/or remedy for thrombosis or embolism.

Use of the compound of the present invention as a pharmaceutical can therefore treat or prevent various diseases caused by a thrombus or embolus such as cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization, formation of a thrombus upon extracorporeal circulation or coagulation upon blood collection.